1 TITLE PAGE

CLINICAL STUDY PROTOCOL

Study Protocol Number:	H3B-6527-G000-101
Study Protocol Title:	An Open-Label Multicenter Phase 1 Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of H3B-6527 in Subjects With Advanced Hepatocellular Carcinoma
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Investigational Product Name:	H3B-6527
Indication:	Advanced Hepatocellular Carcinoma
Phase:	1

Approval Date:	Original Protocol	15 Mar 2016
	Amendment 01	29 Apr 2016
	Amendment 01.1	12 May 2016
	Amendment 02	06 Oct 2016
	Amendment 03	15 Dec 2016
	Amendment 04	31 May 2017
	Amendment 04.1	14 Jun 2017
	Amendment 05	06 Jul 2017
	Amendment 06	22 Feb 2018
	Amendment 07	14 Nov 2018
	Amendment 08	28 Aug 2019
	Amendment 09	30 Sep 2020
IND Number:	128686	
EudraCT Number:	2016-001915-19	
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.	
Confidentiality Statement:	This document is confidential. It contains proprietary information of H3 Biomedicine, Inc and Eisai (the Sponsors). Any viewing or disclosure of such information that is not authorized in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.	

DATE	Highlights of Major Changes Section/Change
15 Mar 2016	Original Protocol
29 Apr 2016	Amendment 01
	Title Page: - Added Amendment 01 and the EudraCT number - Changed address of the location of the Oncology Business Group
	Corrected typographical errors in the following sections: - Section 2 - changed OT**C** to OT**V** - Section 7.1 – deleted extra () - Section 2 (Clinical Study Synopsis) and Section 9.3.1 – added missing parenthesis to Inclusion Criteria 13. - Section 9.4.4.1, Table 3 – deleted duplicate word (“in”) - Section 9.4.8 - added missing parenthesis after the word “consent” - Section 9.5.1.4.1 – added missing parenthesis before the word “whichever”
	In Section 2 (Clinical Study Synopsis) and Section 9.3.2 - deleted Exclusion criterion 1 with renumbering of remaining exclusion criteria
	Edited text in Section 5.1: - to include the option for **electronic study approval** by the IRB/IEC chairman. - to allow the **Sponsor’s designee** to notify the IRB/IEC at the end of the study **if required**.
	Added text to Section 9.1.1.1 and Section 9.4.4.1 to clarify that if ≥2 subjects within a cohort experience a DLT and the previous dose level did not enroll 6 subjects, enrollment will move down to the previous dose level and continue until 6 subjects are enrolled; the same guidelines for determining the MTD will be followed.
	Edited text for consistency throughout the protocol (Section 2 [Clinical Study Synopsis]; Section 9.1.2.3, Section 9.1.2.4, and Section 9.5.5) to clarify that a subject can continue to receive study treatment after disease progression if they demonstrate clinical benefit as determined by the investigator after discussion with the Sponsor.
	Edited text in Section 2 and Section 9.5.1.2.1 to clarify when brain scans are required to be performed.
	Edited text in the Section 2 and Section 9.5.1.3.3 to indicate that paired-skin biopsies are optional.
	Edited Table 6 as follows: - Table format changed to ensure that table heading rows do not appear on footnote pages. - Deleted requirement for ECGs on Cycle 1 Day 8 and Cycle 1 Day 15 - Edited Footnote “i” to clarify timing of ECGs during Dose Escalation

DATE	Highlights of Major Changes Section/Change
	- Deleted row containing Bile Acids - Edited Footnote "k" to clarify that measurement of total bile salts is done as part of the safety blood chemistry panel. - Added row to clarify timing of brain scans. Edited table footnotes as required. - Edited footnote "t" to indicate that paired-skin biopsies are optional.
	Edited Table 7 as follows: - Deleted requirement for ECGs to be performed on Cycle 1 Day 8 and Cycle 1 Day 15 - Edited Footnote "j" to clarify timing of ECGs in the Food Effect and Expansion Cohorts. - Deleted row containing Bile Acids. - Edited Footnote "k" to clarify that measurement of total bile salts is done as part of the safety blood chemistry panel. - Added row to clarify timing of brain scans. Edited table footnotes as required. - Edited Footnote "t" to indicate that paired-skin biopsies are optional.
12 May 2016	Exclusion criteria numbers 9 and 10 were added to the Synopsis and Section to specify that: - Subjects taking a strong inhibitor or inducer of CYP3A4 enzyme within at least 2 weeks before the start of the study drug and during the conduct of the study unless there was an emergent or life threatening medical condition that required it (exclusion criterion number 9), and - Subjects taking any drug known to prolong QTc interval within at least 2 weeks before the start of the study drug and during the conduct of the study (exclusion criterion number 10) Are excluded from enrollment into the study.
	Subjects were instructed to follow the storage requirements listed on the study drug label (Section 9.4.3.4)
	Tables 6 and 7, Schedule of Assessments - Edited Footnote "o" of Table 6 and Footnote "n" of Table 7 to clarify PK the 24 h sampling time will be collected prior to the next dose.
	Table 7, Schedule of Assessments - Added an 'X' for collection of a hematology laboratory sample to ensure collection of hematology laboratory sample at the Screening Visit.
	Appendix 5, item number 2 of Urine Samples for Metabolism Profiling, was updated to remove the requirement of a preweighted stainless steel container for collection of urine samples.

DATE	Highlights of Major Changes Section/Change
06 Oct 2016	Amendment 02
	Global: Revised protocol to remove enrollment of subjects with intrahepatic cholangiocarcinoma (IHCC) and all corresponding text.
	Global: Removed reference to subjects with/without cirrhosis
	Global: Changed "Part 2, 3-arm Cohort Expansion," to "Part 2, Expansion phase"
	List of Abbreviations: Updated to reflect changes to protocol
	Section 6: Revised to clarify Eisai's role in the conduct of the study
	Section 6 and Synopsis: Revised to reflect increase in the number of anticipated participating sites from 20 to 25
	Section 7.1.1.1: Included statement that data from ongoing preclinical studies show tumor regression has been observed in xenograft mouse models having undetectable levels of FGF19.
	Sections 7.2, 9.1, 9.1.1.3, 9.2, and 9.4.4.3, Table 8, and Synopsis: Revised protocol to clarify that the first 12 subjects enrolled in the Expansion phase will participate in the Food Effect part of the study
	Section 7.2 and Synopsis: Revised protocol so that subjects with or without elevated baseline levels of FGF19 could be enrolled in the Expansion phase.
	Section 8.2, Table 8 in Section 9.5.2, and Synopsis: Clarified that subjects with or without elevated levels of FGF19 could be enrolled in the study.
	Sections 8.2, 9.1.1.2, and Synopsis: Clarified that FGF19 concentration would be determined by a Sponsor-designated laboratory.
	Sections 8.3, 9.5.1.3.3, 9.7.1.1, Table 7 and Table 8, and Synopsis: Removed the requirement to perform skin biopsies and the measurement of FGF19 levels in skin as an exploratory endpoint.
	Sections 9.1, 9.1.1.2, and Synopsis: Increased enrollment in the Expansion phase to 60 subjects (including a minimum of 20 subjects with tumors expressing elevated levels of FGF19).
	Table 1 in Section 9.1.1.1 and Synopsis: Removed reference to determination of the MTD by subpopulation and added a footnote to show that 300 mg QD is the planned starting dose level
	Table 2 in Section 9.1.1.1.1, Section 9.7.1.8, and Synopsis: Added language for drug-related Grade 2 nonhematologic toxicities that required dose modification; changed subject eligibility requirement for determination of DLTs from completion of 17 days to 14 days of treatment; deleted all footnotes in Table 2 and made minor grammatical changes for consistency throughout table
	Section 9.1.1.3: Added new Figure 1, *Dosing Schema for Food Effect Cohort*

06 Oct 2016 (continued)	Sections 9.1.2.4, 9.5.1.2.2, 9.5.5, and Synopsis: Text revised to reflect that subjects will be followed for survival every 6 weeks; clarified that termination of the study will occur 18 months after enrollment of the last subject.
	Sections 9.3, 9.7.2, and Synopsis: Total sample size changed from 60-90 subjects to 78 to 90 subjects, including 60 subjects in the Expansion phase
	Section 9.3.1 and Synopsis: Revised inclusion criteria nos. 2, 3, 4, 7, and 8 per changes to included population and mRECIST; minor grammatical changes for consistency
	Section 9.3.2 and Synopsis: Removed exclusion criterion no. 19 (pregnancy and lactation) and renumbered subsequent criteria; minor grammatical changes made to criteria nos. 6, 8, 9, and 22.
	Sections 9.4.4.1, 9.5.5, 9.7.1.8 and Synopsis: Revised text to clarify subjects eligible for determination of DLTs
	Section 9.4.8.1 and Synopsis: Added strong inducers/inhibitors of CYP3A4 as prohibited concomitant medication; changed text to prohibit the use of any long-acting proton pump inhibitors; added new Table 5, *Inducers and Strong Inhibitors of CYP3A4*
	Section 9.5.1.2.1 and Synopsis: Clarified procedure for retention of tumor scans
	Section 9.5.1.3.1: Clarified that a nonvalidated assay such as matrix-assisted laser desorption/ionization will be used to measure H3B-6527 concentration in tumor tissue
	Sections 9.5.1.3.3 and Synopsis: Revised the procedure for tumor biopsies. Clarified that all subjects with elevated baseline levels of FGF19 in the Expansion phase will undergo paired tumor biopsies, with one taken predose (any time during Screening before the first dose of H3B-6527 on C1 Day 1) and one taken approximately 3 hours (±2 h) postdose on C2 Day 1.
	Sections 9.5.1.3.3, 9.7.1.1, Table 7 and Table 8, and Synopsis: Removed the requirement to perform skin biopsies and the measurement of FGF19 levels in skin as an exploratory endpoint.
	Section 9.5.2, Schedules of Assessments: Added visit windows; clarified PK, PD and urine collection times, posttreatment procedures, and time points for survival follow-up; revised the footnotes pertaining to the timing for paired tumor biopsies. Tables 6 and 7 were renumbered Tables 7 and 8.
	Section 9.5.5: Revised criteria for subjects who are and are not evaluable for DLT assessments
	Section 9.7.1.1 and Synopsis: Revised criteria for determining objective response rate (ORR)
	Sections 9.7.1.2 and Synopsis: Redefined the Full Analysis Set
	Section 9.7.1.6: Removed definition for the calculation of ORR

	List of References; Updated citation for Nexavar prescribing information; added new reference: Hagel, et al., 2015.; deleted references Sia D, et al., 2013 and Churi CR, et al., 2014
06 Oct 2016 (continued)	Removed Appendix 2, *Response Evaluation Criteria in Solid Tumors (Subjects with IHCC)*; renumbered subsequent appendices accordingly
15 Dec 2016	Amendment 03
	Revised the criteria for Grade 4 GI dose-limiting toxicities (ie, diarrhea and vomiting) in Table 2 (Section 9.1.1.1.1) and Synopsis per the FDA's recommendation
14 Jun 2017	Amendment 04.1 (country-specific to South Korea)
	Section 9.3.2 and Synopsis: Added exclusion criteria # 22 to exclude subjects with inorganic phosphorus > upper limit of normal for the institution, per South Korea health authority request.
	Section 9.3.2 and Synopsis: Added exclusion criteria # 23 to exclude subjects with total or ionized serum calcium > upper limit of normal for the institution, per South Korea health authority request.
	Section 9.3.2 and Synopsis: Added exclusion criteria # 24 to exclude subjects with endocrine changes that may result in increases in calcium or phosphate, including but not limited to hyperparathyroidism and tumoral calcinosis, per South Korea health authority request.
	Section 9.3.2 and Synopsis: Added exclusion criteria # 25 to exclude subjects with past medical history and/or current evidence of tumoral calcinosis, per South Korea health authority request.
	Section 9.3.2 and Synopsis: Added exclusion criteria # 26 to exclude subjects who take calcium, vitamin D or systemic corticosteroids, per South Korea health authority request.
	Section 9.4.8.1 to include drugs that raise serum calcium and phosphorus levels (eg, vitamin D supplements, calcium dietary supplements, calcium antacids, etc.) and systemic corticosteroids as prohibited medications, per South Korea health authority request.
	Section 9.4.8.2 and Synopsis: Added language to clarify management of hyperphosphatemia or hypercalcemia, per South Korea health authority request.
06 Jul 2017	Amendment 05
	Global: Revised protocol to include enrollment of subjects with intrahepatic cholangiocarcinoma (ICC). Rationale: new article by Yoo et. al. (2017) shows that ICC has genomic alterations in FGF19 that are very similar to HCC and FGF19/FGFR4 could also potentially play a critical role in ICC.
	List of Abbreviations: Updated to reflect changes to protocol (addition of ICC).
	Section 5.3: Removed sentence "Subjects will be required to provide separate informed consent for the collection of samples for pharmacogenomics (PG); see Section 9.5.1.3.4."; in Section 9.5.1.3.4: Removed portion of sentence stating that PG samples are collected "from all subjects who provide consent to have

	such samples collected." Rationale: subjects are consented for PG sample collection in the main ICF (no separate ICF required).
	Sections 7.2, 9.1, 9.1.1.3, 9.2, 9.4.4.3, Table 8, and Synopsis: clarified that the food effect cohort will be comprised of the first 12 HCC subjects enrolled in dose expansion. Rationale: food effect may be different for ICC subjects compared with HCC subjects.
	Section 9.1.1.1 and Synopsis: revised protocol to allow for intrapatient dose escalation during dose escalation. Rationale: The possibility of intrapatient dose escalation theoretically reduces the number of subjects who are treated at sub-therapeutic doses. Permitting intrapatient dose escalation gives some subjects the opportunity to be treated at higher and presumably more effective doses.
	Section 9.1.1.1 and Synopsis: revised protocol to clarify that once the MTD/RP2D is reached, at least 6 HCC subjects must be enrolled at the RP2D (regardless of the total number of subjects enrolled at that dose level) in order to proceed with dose expansion. As subjects with ICC may have a better tolerability than subjects with HCC, the SRC may decide to continue dose escalation for ICC subjects after the RP2D has been established for HCC subjects.
	Table 2 and Synopsis: Revised DLT definition to include subjects with CTCAE Grade 3 anemia if transfused or if lasting for more than 7 days, or CTCAE Grade 4 anemia of any duration, per Taiwan health authority request.
	Table 2 and Synopsis: Revised DLT definition to clarify that for subjects with a starting ALT within the normal range for the local laboratory, an elevation ALT $\geq 5 \times$ ULN for the local laboratory will be considered a DLT; for subjects with an abnormal value $\geq$ ULN at baseline based on the local laboratory ranges, an ALT elevation $\geq 10 \times$ ULN for the local laboratory will be considered a DLT, per Taiwan health authority request.
	Section 9.3.1 and Synopsis: Revised inclusion criteria # 3, 4, and 8 per changes to included population and RECIST 1.1.
	Section 9.3.2 and Synopsis: Added clarifications to exclusion criteria # 22, 23, 24, 25, and 26.
	Section 9.4.3.4: Updated study drug storage conditions to clarify that study drug should be stored refrigerated at 2-8°C at the study center due to availability of stability data for refrigerated conditions.
	Section 9.4.8.1: added systemic corticosteroids to prohibited medications and clarification of systemic corticosteroid washout period.
	Section 9.4.8.2 and Synopsis: Added minor language clarifications to management of hyperphosphatemia or hypercalcemia section.
	Section 9.5.1.3.3, Synopsis, Table 7, and Table 8: Clarified that tumor biopsy samples should not be formalin fixed paraffin embedded, for consistency with collection instructions in the lab manual.

	Table 7 and Table 8: updated footnotes to clarify that the ±3 day-window for C1D8 does not apply to the PK sampling (administrative change).
	List of References: added new references: Sia, et al, 2013, Churi, et al., 2014, and Yoo, et al., 2017 to support inclusion of ICC subjects.
	Added Appendix 2, Response Evaluation Criteria in Solid Tumors (Subjects with ICC); renumbered subsequent appendices accordingly
22 Feb 2018	Amendment 06
	Global edits applied to conform with Eisai Writing Style Guideline (eg, parallel structure of bulleted lists, *P* value, capitalization and spacing).
	Section 7.2: Edited to remove reference to the food-effect portion of the study, which will no longer be included in the current study. The effect of food on the bioavailability of H3B-6527 will be assessed in a separate, concurrent clinical study, H3B-6527-A001-001: A Randomized Phase 1 Food-Effect Study of H3B-6527 in Healthy Subjects. Conditional language has been added to indicate that subjects may be asked to take study drug in conjunction with a meal depending on study results from this Healthy Volunteer Food Effect (HVFE) study.
	Section 8.2: Removed the objective to determine whether a high-fat meal had any effect on bioavailability since sufficient data will be obtained from HVFE study to support administration with or without food in the current study.
	Section 9.1: Edits to clarify the dose schedules and sample size for the dose escalation and expansion portions of the study and to allow simultaneous exploration of QD and BID dosing schedules.
	Figure 1: Add this study diagram to clarify the overall study design between Parts 1 and 2 of the study, including the number of subjects planned for enrollment.
	Section 9.1.1.1: Added a statement to further clarify that the selection of the RP2D will be based on an integrated evaluation of safety and tolerability, as well as PD and PK data to allow flexibility in study design and dosing schedule. Added a statement to clarify that subjects who experience a dose-limiting toxicity (DLT) or dose-modifying event (an adverse event that meet the criteria for a DLT but occurring after Cycle 1) have the option for resuming treatment at a reduced dose following resolution of the event and joint consultation between the investigator and the Sponsor as to what is in the best clinical interest of the subject as previously outlined in Section 9.4.2.
	Table 1: Revised the table footnote to include potential for a BID dose schedule and to allow greater flexibility with BID dose schedule or alternate dosing options. Revised the table to reflect the total daily dose amounts so as to include the BID dose schedule.
	Table 2: Updated table caption (this was Table 2). Minor correction to the CTC AE Grade 3 bilirubin to specify that it must be >3 ×ULN (not ≥3 ×ULN) to align with CTCAE v4.03.

	Section 9.1.1.2: Expanded this section to include additional study design details regarding the QD and BID dose schedules and to discuss the overall number of subjects to be recruited for this part of the study.
	Section 9.1.1.3: Deleted this section since the food effect cohort will no longer be applicable for this study.
	Section 9.2: Added additional information about food recommendations for the study. If study drug plasma exposure is found to be increased with food (based on the HVFE study), this section included a few details about how study drug would be administered with food, including details about fasting for PK/PD testing prior to study drug administration. This text helps to clarify important criteria if study drug administration is to occur in conjunction with a meal.
	Section 9.3: Revised the total number of subjects to be enrolled in the study based upon changes to the study design for Parts 1 and 2.
	Sections 9.3.1 and 9.3.2 General: Edits to reflect parallel construction to adhere to the Eisai Writing Style Guide.
	Section 9.3.1 #3: Revised this bullet to allow for noninvasive diagnosis of HCC and to further clarify criteria to be used. Also added a sub-bullet to clarify that eligible subjects must have had at least one prior standard-of-care therapy or declined such therapy given the changing treatment landscape in this subject population.
	Section 9.3.1 #5: New criterion to indicate that all subjects must be FGF19-positive, as determined by Sponsor-designated laboratory prior to enrollment in the Dose Expansion phase of the study.
	Section 9.3.1 #6: Added a window for the receipt of prior chemotherapy or immunotherapy to include 4 weeks or 5 half-lives (whichever is shorter).
	Section 9.3.1 #7: Edit to clarify the washout period for radiopharmaceuticals from “within 8 weeks” to “8 weeks before study drug administration.”
	Section 9.3.2 #1: Revised this criterion to indicate that subjects with stage 1 prostate cancer are eligible for study participation.
	Section 9.3.2 #11: Revised this criterion to remove specific reference to “long-acting” PPIs. Additionally, added a statement to allow antacid use during the study with the exception of calcium carbonate antacids, which could interfere with calcium levels.
	Section 9.3.2 #13: Removed selective pan-FGFR inhibitor as an exclusionary previous treatment.
	Section 9.3.2 #14: Clarified that only live vaccines are prohibited.
	Section 9.4.2: Added a statement to discuss DLTs and to specify when a subject may continue on treatment at a reduced dose following a DLT.
	Section 9.4.4.1: Clarified the threshold for subjects to be evaluable as 17 of 21 days (80%) to accommodate the potential for a BID dose schedule.

	Section 9.4.4.3: Removed this food effect cohort, which will no longer be included in the current study. The effect of food on the bioavailability of H3B-6527 will be assessed in a separate, concurrent clinical study, H3B-6527-A001-001: A Randomized Phase 1 Food-Effect Study of H3B-6527 in Healthy Subjects. Conditional language has been added to indicate that subjects may be asked to take study drug in conjunction with a meal depending on study results from this HVFE study as needed.
	Section 9.4.6: Added a sentence to clarify guidance on missed doses, particularly for the BID schedule.
	Section 9.4.8: Added language to specify that study drug must be withheld if a subject requires a short course of steroids while on-treatment.
	Section 9.4.9: Removed some of the restrictions that were included in this section for the food effect cohort since that is no longer being included for reasons stated above. Subjects are still required to limit physical activity immediately before and after blood draws.
	Section 9.5.1.1.1: Added this section to discuss prescreening requirements for subjects and to include that an optional separate consent may be used to screen subjects and collect tumor tissue samples.
	Section 9.5.1.1.3: Revised the medical history to specifically state the collection of disease history of portal vein invasion or thrombosis.
	Section 9.5.1.3.3: Revised this section to state that a separate consent may be used to allow screening of tumor tissue samples prior to enrollment and to include a visit window for the collection of the second tumor biopsy sample.
	Section 9.5.1.4.3: Revised this section to remove specific reference to the requirement to review bile salts/acids prior to study drug administration since turnaround time for results precludes real-time review. However, results will be reviewed by the site team when available, and in aggregate to look for any potential safety trends as outlined in the existing safety review plan.
	Section 9.5.1.4.5: Added language to the OCT examination to clarify that any abnormalities would be recorded as AEs and to provide a window for the completion of the examination prior to Day 1 of each specified cycle.
	Section 9.5.1.4.6: Revised this section to include appropriate windows/timing for Holter monitoring to be consistent with the ECG manual.
	Section 9.5.1.4.9: Revised the sentence on pregnancy testing to include flexibility for urine or serum pregnancy testing before the first dose and at OTV.
	Tables 6 and 7: Additional edits were made to the schedule of events to adhere to edits made in the protocol text.
	Section 9.7.1.1: Updated the study endpoints to clarify that ORR is determined by a best overall confirmed response of CR or PR. Clarified that confirmed progression is not required for DOR and PFS.

	Section 9.7.2: Revisions here to encompass decisions made regarding overall study design in the Dose Expansion Phase, including the removal of the food effect cohort, the inclusion of 2 separate treatment arms and fixed sample sizes for both arms in expansion.
	Tables 8 and 9: Added two tables to depict the dose schedules in the Dose Expansion arm and the precision estimates for ORR of 30% in 40 subjects.
	Section 9.7.3: Added a statement that database locks are not required for interim analysis and clarified that PK summaries may also be periodically provided.
	Section 10: European Medicine Agency (2012) reference on drug interactions and Food and Drug Administration (2002) reference on food interactions was removed since the food effect portion of the study was removed. Hagel (2015) was removed from this list following the edits applied to the statistical sample size section.
	Section 12: Added Appendix 7, Child-Pugh scoring as it is part of the eligibility requirements for subjects in the study.
14 Nov 2018	Amendment 07
	Section 9.3.1 #3: Revised sub-bullet to clarify that eligible subjects must have had at least one prior standard-of-care therapy, unless contraindicated.
28 Aug 2019	Amendment 08
	Global: Revised protocol to remove enrollment of subjects with intrahepatic cholangiocarcinoma (ICC) and all corresponding text. Data indicates that fibroblast growth factor 19 (FGF19) is not a driver in ICC, and that fibroblast growth factor receptor 4 (FGFR4) dependence is likewise not observed in ICC.
	List of Abbreviations: Updated to reflect changes to protocol.
	Section 5.3: Revised to indicate that subjects will be asked to sign an informed consent form (ICF) up to 8 weeks before the first dose of study drug.
	Section 5.3: Removed the mention of the separate consent form for the collection of tumor tissue for screening purposes prior to enrollment as the collection of tumor tissue will be conducted with the ICF signing up to 8 weeks before the first dose of study drug.
	Section 8.3: Revised the exploratory biomarkers to remove the assessment of the pharmacodynamic effects of phospho-extracellular-signal-regulated kinases (pERK) and cytochrome P450 (CYP) 7A1 and other FGFR4-related biomarkers in tumor samples, as the in-treatment biopsy will not be collected.

Synopsis, Section 9.1, and Section 9.2: Updated the study design to indicate that subjects will be administered the study drug with food based on the Healthy Volunteers Food-Effect study (Study H3B-6527-A001-001: A Randomized Phase 1 Food-Effect Study of H3B-6527 in Healthy Subjects). Also, the starting dose of study drug when given with food was agreed upon with the Safety Review Committee to meet the criteria that it be no more than one-half of the previously determined safe total daily dose level and that any additional dose escalation will follow the procedures outlined in Section 9.1.1.
Section 9.1.1.1: Added a statement that information about DLTs or safety concerns to all sites will be communicated by the Sponsor as per the separate Dose Escalation Plan.
Synopsis and Section 9.1.1.1.1: Included the definition of dose-modifying events to the section and Table 2 as any event that occurs in Cycle 2 or beyond (including any cycle in Phase 2).
Section 9.1.1.1.1 and Table 2: Added aspartate aminotransferase (AST) to the criteria for hepatic toxicity.
Synopsis and Section 9.1.2.1: Removed "to obtain informed consent" from the 28-day Screening Period as the ICF signing will be up to 8 weeks before the first dose of study drug.
Section 9.2: Clarified that subjects will be required to fast 2 hours prior to pharmacodynamic assessments.
Synopsis and Section 9.3.1: Revised inclusion criteria number 4 to reflect that the tumor sample is collected up to 8 weeks before administration of study drug.
Synopsis and Section 9.3.1: Revised inclusion criteria number 7, Part 2, Dose Expansion, to indicate that the fresh tumor tissue must be available and collected up to 8 weeks before administration of H3B-6527 on Cycle 1 Day 1.
Synopsis and Section 9.3.1: Revised inclusion criteria number 14 to define sexual abstinence in accordance with the Clinical Trial Facilitation Group guidance.
Synopsis and Section 9.3.2: Revised exclusion criteria number 9 to include the mention of the P-glycoprotein transporter.
Synopsis and Section 9.3.2: Revised exclusion criteria number 16 to replace corrected QT (QTc) >500 ms with QTc >450 ms, as >500 ms is considered a Grade 3 QTc prolongation as per Common Terminology Criteria for Adverse Events (CTCAE).
Synopsis and Section 9.3.2: Added exclusion criteria number 27, "Hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose galactose malabsorption."
Section 9.4.6: Revised to indicate that subjects will be instructed to take the dose in conjunction with a meal.
Synopsis and Section 9.4.8.1: Revised the list of prohibited concomitant therapy and procedures to include P-glycoprotein transporter

Section 9.5.1: Revised to indicate that all subjects must provide written informed consent up to 8 weeks before the first dose of study drug.
Section 9.5.1.1.1: Revised to indicate that a fresh tumor biopsy, the signing of the ICF, and the collection of blood samples for pharmacodynamic analysis (same day as fresh tumor biopsy) will be required up to 8 weeks before administration of H3B-6527 on Cycle 1 (C1) Day 1, in order to enroll in the Dose Expansion Phase of the study. The 28-day Screening Period will begin when any of the remaining screening assessments are performed. The entire Pretreatment Phase must be completed within 8 weeks of study drug administration on C1 Day 1.
Synopsis and Section 9.5.1.2.1: Revised to indicate that a brain scan should be performed for all subjects as clinically indicated.
Section 9.5.1.3.3: Removed the mention of a separate consent form for screening purposes, as a fresh tumor biopsy, the signing of the ICF, and the collection of blood samples for pharmacodynamic analysis (same day as fresh tumor biopsy) will be required up to 8 weeks before study drug administration.
Synopsis and Section 9.5.1.3.3: Revised to indicate that the signing of the ICF, the collection of blood samples for pharmacodynamic analysis (same day as fresh tumor biopsy), and a fresh tumor tissue sample is required to be collected up to 8 weeks before administration of the first dose of H3B-6527 on C1 Day 1. The 28-day Screening Period will begin when any of the remaining screening assessments are performed.
Synopsis and Section 9.5.1.3.3: Removed the requirement of paired tumor biopsies for the Dose Expansion phase.
Section 9.5.1.4.1: Corrected the adverse event and serious adverse event collection timeframe to be within 30 days after the last study drug dose.
Section 9.5.1.4.5: Added a statement to indicate that ophthalmic examinations performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen.
Section 9.5.1.4.6: Revised to indicate that all subjects in the dose expansion phase of the study will have a single 12-lead safety electrocardiogram (ECG) performed at Screening or Baseline (single unless abnormalities are observed or otherwise clinically indicated, in which case ECGs will be performed in triplicate at 2-minute intervals), Day 1 of each cycle (pre- and post-dose), and at the Off-treatment Visit (OTV).
Section 9.5.1.4.8: Added a statement to indicate that multiple-gate acquisition (MUGA) scans or echocardiograms performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen.
Section 9.5.2, Table 6: Added footnote “a” to the screening column of informed consent, as it indicates that the signing of the ICF may be up to 8 weeks before the first dose of study drug.
Section 9.5.2, Table 6: Added “if clinically indicated” to the Treatment and Extension columns of Echocardiogram/MUGA to reflect the corresponding footnote.

Section 9.5.2, Table 6: Removed the statement, "Subjects will be fasted 2 hours before and 2 hours after dose," from the Treatment and Extension columns of H3B-6527 administration to reflect the corresponding revised footnote "y" that H3B-6527 should be taken in conjunction with a meal.
Section 9.5.2, Table 6: For footnote "f," added a statement to indicate that ophthalmic examinations performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen.
Section 9.5.2, Table 6: For footnote "g," added a statement to indicate that MUGA scans or echocardiograms performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen.
Section 9.5.2, Table 6: For footnote "j," revised to indicate that 12-lead ECGs will be collected at the following time points: Screening (single) or Baseline (single unless abnormalities are observed or if clinically indicated, then in triplicate at 2-minute intervals); Day 1 of all cycles (before and after study drug administration); and at the OTV.
Section 9.5.2, Table 6: For footnotes "q" and "r," clarified that all subjects will be required to fast 2 hours prior to those assessments.
Section 9.5.2, Table 6: For footnote "s," removed the mention of the separate consent form for screening of sample tumor tissue.
Section 9.5.2, Table 6: For footnote "u," revised to state that the screening computed tomography (CT)/magnetic resonance imaging (MRI) of the brain should be performed as clinically indicated.
Section 9.5.2, Table 6: For footnote "y," revised to state that H3B-6527 should be taken daily at the assigned schedule and dose in conjunction with a meal.
Section 9.5.2, Table 7: For the Extension phase, corrected the Visit column for Day 8 to reflect odd numbered visits.
Section 9.5.2, Table 7: Added footnote "a" to the screening column of informed consent, pharmacodynamic blood samples, and fresh tumor tissue biopsy, as the footnote indicates that those procedures/assessments may be up to 8 weeks before the first dose of study drug.
Section 9.5.2, Table 7: Added "if clinically indicated" to the Treatment and Extension columns of Echocardiogram/MUGA to reflect the corresponding footnote.
Section 9.5.2, Table 7: Removed the row for in-treatment tumor tissue biopsy and the corresponding footnote "r."
Section 9.5.2, Table 7: For footnote "a," revised to state that the Screening Period extends from Day -28 to Day -1, except for signing of the ICF, the fresh tumor tissue biopsy, and the blood samples for pharmacodynamic analysis, which may be up to 8 weeks before the first dose of study drug. The 28-day Screening Period will begin when any of the remaining screening assessments are performed.

	Section 9.5.2, Table 7: For footnote "e," added a statement to indicate that ophthalmic examinations performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen.
	Section 9.5.2, Table 7: For footnote "f," added a statement to indicate that MUGA scans or echocardiograms performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen.
	Section 9.5.2, Table 7: For footnote "i," revised to indicate that 12-lead ECGs will be collected at the following time points: Screening (single) or Baseline (single unless abnormalities are observed or if clinically indicated, then in triplicate at 2-minute intervals); Day 1 of all cycles (before and after study drug administration); and at the OTV.
	Section 9.5.2, Table 7: For footnotes "n" and "o," clarified that all subjects will be required to fast 2 hours prior to those assessments.
	Section 9.5.2, Table 7: For footnote "p," removed the mention of the separate consent form for screening of tumor tissue.
	Section 9.5.2, Table 7: For footnote "q," revised to state that a fresh tumor tissue sample is required to be collected up to 8 weeks before administration of H3B-6527 on C1 Day 1.
	Section 9.5.2, Table 7: For footnote "r," revised to state that the screening CT/MRI of the brain should be performed as clinically indicated.
	Section 9.5.2, Table 7: For footnote "v," revised to state that all subjects in the Expansion phase will take H3B-6527 daily in conjunction with a meal.
	Section 9.5.5: Corrected the number of days that would allow for subject replacement to at least 17 of 21 days.
	Section 10, Reference List: Updated to reflect changes to protocol
	Removed Appendix 2 Response Evaluation Criteria in Solid Tumors (Subjects with ICC).
	Appendix 4: For urine samples for metabolite profiling, removed the recording of mass of urine from the case report form, as the total volume is recorded.
30 Sep 2020	Amendment 09
	Synopsis, Section 9.1.2.4, Section 9.5.1.2.2, Section 9.5.2 (Table 6 [footnote z] and Table 7 [footnote w]), and Section 9.5.5: Updated survival follow-up language.
	Synopsis and Section 9.1.2.4: Specified when data cutoff for the primary analysis will occur.
	Synopsis and Section 9.1.2.4: Defined end of study as when the last ongoing subject completes their off treatment visit.
	Synopsis, Section 9.1.2.4: Clarified that the off treatment visit should occur 30 days after final dose with a window of ± 3 days.

	Synopsis, Section 9.5.1.4.6, and Section 9.5.2 (Table 6 [footnote j] and Table 7 [footnote i]): Updated language concerning ECG assessments.
	Section 9.5.2 (Table 6 [footnotes q, r] and Table 7 [footnotes n, o]): Updated language for collection of biomarker samples.
	Section 9.7.1.2: Clarified that summary of efficacy will be based on the Full Analysis Set for HCC subjects, and that the Response Evaluable Set will only include HCC subjects.
	Section 9.7.1.6: Clarified that efficacy analysis will be performed at the time of data cutoff for primary analysis. Clarified that all efficacy parameters will be summarized for the Full Analysis Set for HCC subjects. Clarified that ORR, duration of response, and time to response will also be summarized for the Response Evaluable Set as appropriate.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No. H3B-6527

Name of Active Ingredient: N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide

Study Protocol Title

An Open-Label Multicenter Phase 1 Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of H3B-6527 in Subjects With Advanced Hepatocellular Carcinoma

Investigators

Multiple investigators

Sites

Up to approximately 40 sites planned globally

Study Period and Phase of Development

Approximately 48 months

Phase 1

Objectives

Primary objectives

- Determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of H3B-6527 in subjects with advanced hepatocellular carcinoma (HCC)
- Assess the safety and tolerability of H3B-6527 as a single agent administered orally

Secondary objectives

- Evaluate the pharmacokinetic (PK) profile of H3B-6527
- Evaluate the preliminary antitumor activity of H3B-6527 at the RP2D and schedule in subjects with advanced HCC who are fibroblast growth factor 19 (FGF19)-positive as determined by the Sponsor-designated laboratory

Exploratory objectives

- Explore biomarkers and their correlation with safety and efficacy endpoints
- Assess the pharmacodynamic effects of H3B-6527 on FGF19, Ki67, bile acids, and other fibroblast growth factor receptor 4 (FGFR4)-related biomarkers in blood
- Explore the relationship between PK and pharmacodynamics
- Exposure to H3B-6527 in tumor samples may be assessed
- Explore the metabolite profile of H3B-6527 in plasma and urine

Study Design

This is an open-label, multicenter, Phase 1 study that will be conducted in 2 parts, a Dose Escalation phase (Part 1) and a Dose Expansion phase (Part 2). Approximately 30 to 128 are planned for enrollment.

Dose escalation will follow a standard 3+3 cohort design until the MTD/RP2D for each dosing schedule is determined in this population.

H3B-6527 will be administered as a single-agent by oral administration in 21-day cycles without break to examine both once daily (QD) and twice daily (BID) dosing schedules, with flexibility to also examine additional alternate dosing schedules. The study drug will be administered with food based on the Healthy Volunteers Food-Effect study (Study H3B-6527-A001-001: A Randomized Phase 1 Food-Effect Study of H3B-6527 in Healthy Subjects). The starting dose of study drug when given with food was agreed upon with the Safety Review Committee (SRC) to meet the criteria that it be no more than one-half of the previously determined safe total daily dose level. Any additional dose escalation will follow the procedures outlined in Section 9.1.1.

Safety, tumor response, PK, and pharmacodynamic assessments will be performed for every subject; details are described under **Assessments**.

This study makes provision for exploring a BID schedule of H3B-6527 if evaluation of the PK, pharmacodynamics, or safety of H3B-6527 suggests that it may be preferable to administer H3B-6527 BID rather than QD. The criteria to evaluate a BID schedule will be based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all dose levels tested. In this case, a new cohort of 3 subjects will be enrolled and treated with a BID dose. The initial total daily dose given BID will be equal to a total daily dose that has been well tolerated as a QD dose (dose-limiting toxicity [DLT] rate < 33% in a cohort of 3-6 subjects). If BID dosing of H3B-6527 is well tolerated in this initial cohort then dose escalation may continue with BID dosing, following the same dose escalation rules applied to QD dosing.

Furthermore, additional cohorts of subjects may be enrolled to evaluate a less frequent dosing schedule (eg, daily for 2 consecutive weeks every 3 weeks [dosing on Days 1-14 of a 21-day cycle]).

Dose Escalation (Part 1)

The objective of Part 1, the Dose Escalation phase is to determine the MTD and/or RP2D of H3B-6527 in subjects with HCC. The total number of subjects to be enrolled will depend on the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD and/or RP2D of H3B-6527. Assuming 5 dose levels will be studied for the QD dose schedule and 3 dose levels for the BID dose schedule and a maximum of 6 subjects will be enrolled per dose level, approximately 30 to 48 subjects may be accrued during dose escalation.

The criteria to evaluate the BID dose schedule will be based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all QD dose levels tested. In this case, a new cohort of 3 subjects will be enrolled and treated with a BID dose. The initial total daily dose given BID will be equal to a total daily dose that has been well tolerated as a QD dose (DLT <33% in a cohort of 3-6 subjects).

Due to the potential for dropouts during the first cycle of treatment (eg, because of early disease progression), a cohort may initially be expanded to include up to 2 additional subjects. However, if these additional subjects are to be enrolled, they must start treatment within 14 days after the third subject enrolled in the cohort was first dosed with H3B-6527. The decision to dose escalate may still

be made after the third subject enrolled to the dose level in question has completed the first cycle (C) of treatment. However, if under these circumstances the decision is made to enroll subjects to a higher dose level, and one of the additional subjects treated at the preceding dose level experiences a DLT in the first cycle of treatment, then further enrollment of subjects to the higher dose level will be suspended until it can be determined whether the preceding dose level exceeds the MTD. In the meantime, subjects enrolled to the higher dose level may continue treatment at that dose if they are tolerating it well, and if continuing treatment is considered appropriate for the toxicity in question.

For dose-escalation purposes, toxicities assigned as DLTs during the first cycle will be assessed. After 3-6 subjects in a cohort have completed C1, all available safety data will be reviewed by the SRC consisting of Sponsor personnel and investigators and the decision to proceed to the next dose cohort will be made jointly. If different dose schedules are explored, decisions regarding dose escalation will be made based on review of data from subjects enrolled in cohorts on the same schedule, however, safety data from alternate schedules may be considered by the SRC. Toxicities will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

Once a subject has completed C3 at the initially assigned dose schedule and dose level (QD or BID), intrapatient dose escalation will be allowed. Only subjects who have not progressed on treatment, and did not have a dose reduction or interruption because of drug-related adverse events (AEs), can escalate to the highest dose level that has completed DLT assessment within that schedule and has been shown to be safe (no DLT in the first 3 subjects or no more than 1 DLT in 6 subjects). Subjects on the intrapatient dose escalation will not be included in the DLT analysis at the higher dose level. The investigator and the medical monitor must agree that dose escalation is appropriate for the subject prior to escalating their H3B-6527 dose level.

The starting dose of 300 mg (first-in-human dose) is the human equivalent dose (HED) of 1/6th of the highest non-severely toxic dose in the dog.

H3B-6527 will be tested in sequential, escalating dose cohorts (n=3 to 6) at the dose levels in the table below. Dose escalation will follow a modified Fibonacci design such that the magnitude of the escalation will decrease as the dose level nears the HED of the highest non-severely toxic dose in dogs (HED ≈ 2000 mg).

Dose Cohorts in H3B-6527 Dose Escalation Phase

Dose level	Initial No. of Subjects	H3B-6527 Total Daily Dose
-1	3	150 mg
1[a]	3	300 mg
2	3	600 mg
3	3	1000 mg
4	3	1400 mg
5	3	2000 mg

These total daily dose levels may be evaluated in QD or BID dose schedules, intermediate dose levels, and in expansion of an existing dose level of up to 12 evaluable subjects following discussions between the Sponsor and the investigators, if supported by evolving safety, tolerability, PK, and pharmacodynamic data.
BID = twice daily, QD = once daily
a: Planned starting dose level for QD schedule.

Subjects will be assigned to a dose level in the order of study entry. Initially, 3 subjects will be enrolled at the starting dose level. If 2 of the 3 subjects experience a DLT then the dose level -1 (one

dose level below starting dose) will be explored. If 1 of the 3 subjects experiences a DLT then the dose will be expanded to 6 subjects. If ≥2 of 6 subjects in the starting dose cohort experience a DLT during the first cycle, then the dose level -1 will be explored.

Dose escalation to the next higher dose may proceed if no DLT is observed in C1 among the first 3 subjects accrued to a cohort. If 1 of 3 subjects in the cohort experiences a DLT, up to a total of 6 subjects will be enrolled. If 2 or more (≥33%) of the 3-6 subjects in a cohort experience a DLT, dose-escalation will cease, and additional subjects will be treated at a lower dose level. Dose escalation will continue until a dose level where ≥2 of 6 subjects experience a DLT.

The MTD is defined as the highest dose at which no more than 1 of 6 subjects experiences a DLT in the dose cohort. The RP2D may not exceed the MTD and will be agreed upon by the SRC based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all dose levels tested. Clinically significant toxicities (eg, chronic Grade 2 toxicities) or AEs that meet the definition of dose limiting but occurring after C1 (dose-modifying events [DME]) may be considered when determining the RP2D. Once the MTD/RP2D is reached, at least 6 HCC subjects must be enrolled at the RP2D (regardless of the total number of subjects enrolled at that dose level) in order to proceed with dose expansion.

Subjects who do not receive study drug for at least 17 of 21 days (approximately 80%; not necessarily consecutively) during the first cycle for reasons not considered to be a DLT by both the investigators and the Sponsor will be replaced. Subjects who are replaced will not be considered evaluable for DLT assessments.

Definition of Dose-Limiting Toxicities or Dose-Modifying Events

DLTs are any of the following toxicities occurring during C1 Phase 1 only and judged by the investigator as related to study drug (ie, assessed as unrelated to disease, intercurrent illness, or concomitant medications). Any event that occurs in C2 or beyond (including any cycle in Phase 2) will be considered a DME.

TOXICITY	**CRITERIA**
Hematology	Febrile neutropenia CTCAE Grade 4 neutropenia that does not resolve to Grade ≤2 within 7 days CTCAE Grade 3 thrombocytopenia requiring transfusion CTCAE Grade 3 thrombocytopenia and clinically significant bleeding CTCAE Grade 4 thrombocytopenia CTCAE Grade 3 anemia if transfused or if lasting for more than 7 days CTCAE Grade 4 anemia of any duration
Gastrointestinal	CTCAE Grade 3 nausea, vomiting and/or diarrhea lasting more than 72 hours despite the use of optimal anti-emetic/antidiarrheal treatment CTCAE Grade 4 diarrhea and/or vomiting irrespective of prophylaxis or appropriate treatment
Renal	CTCAE Grade ≥3 serum creatinine
Hepatic	CTCAE Grade >3 bilirubin and/or AST/ALT ≥10 × ULN For subjects with a starting AST/ALT within the normal range for the local laboratory, an elevation AST/ALT ≥ 5 × ULN for the local laboratory For subjects with an abnormal value ≥ ULN at baseline based on the local laboratory ranges, an AST/ALT elevation ≥ 10 × ULN for the local laboratory
Other AEs not listed above	Nonhematologic toxicities of CTCAE Grade ≥3 except for the following. 1. CTCAE Grade 3 fatigue lasting less than 1 week,

	2. Isolated CTCAE Grade 3 elevations in biochemistry laboratory values without associated clinical symptoms that last for ≤7 days. This includes electrolyte abnormalities that respond to medical intervention. H3B-6527-related, CTCAE Grade 2 nonhematologic toxicities that, in the opinion of the treating investigator, require a dose reduction or discontinuation of study drug, or lead to the subject's failure to complete at least 17 days of study drug administration in C1, may be deemed to be dose-limiting if agreed upon by participating investigators and the Sponsor.

AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, C = Cycle, CTCAE = Common Terminology Criteria for Adverse Events, ULN = Upper limit of normal.

Expansion (Part 2)

Prior to starting the Dose Expansion phase, the investigators and the Sponsor will use safety, efficacy, PK, and pharmacodynamic data obtained during the Dose Escalation Phase, as well as clinical judgement, to jointly determine the dose schedules (e.g., QD and/or BID) to be studied.

During Part 2, the Dose Expansion phase, a sample size of 40 evaluable subjects per dose schedule will be enrolled to examine QD and/or BID dosing of H3B-6527 based on the recommended dose determined from Part 1. For a reference of the precision of ORR estimates, the associated 2-sided 95% CIs for ORR up to 30% for 40 subjects are provided. Subjects enrolled into Part 2, Dose Expansion phase, must be FGF19-positive as defined by Sponsor-designated laboratory.

When both dose schedules are accruing subjects, an alternating enrollment schema into QD and BID dose schedule will be followed.

Study Phases

The study will be conducted in the following 4 phases: Pretreatment Phase, Treatment Phase, Extension Phase, and Follow-up Phase.

Pretreatment Phase

This Pretreatment Phase will last no longer than 28 days and includes:

- A **Screening Period** to establish protocol eligibility.
- A **Baseline Period** to establish disease characteristics before treatment.

Treatment Phase

The Treatment Phase will last for 1 treatment cycle of 21 days.

Subjects who are receiving study drug at the end of the Treatment Phase will continue to receive study drug in the Extension Phase.

Extension Phase

In the Extension Phase, subjects will continue to receive the same treatment and dose they received during the Treatment Phase, provided termination criteria are not met.

Treatment and Extension Phases

Subjects will discontinue study drug at the time of disease progression, development of unacceptable toxicity, withdrawal of consent, or termination of the study by the Sponsor. However, subjects may continue to receive study treatment as long as they demonstrate clinical benefit as judged by the investigator after discussion with the Sponsor or until the end of the study. Disease progression will be determined by the investigator following relevant modified Response Evaluation Criteria in Solid

Tumors (mRECIST) guidelines. The mRECIST for this protocol harmonizes the original mRECIST criteria (Lencioni and Llovet, 2010) using triphasic liver computed tomography (CT)/magnetic resonance imaging (MRI; optimized for precontrast, arterial phase, and portal venous phase) and elements of Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer, et al., 2009).

Follow-up Phase

After the Off-treatment Visit, all subjects who discontinue study treatment, regardless of their reasons for doing so, will be followed for survival approximately every 12 weeks for up to 12 months or until 6 cycles after last patient in, death, loss to follow-up, or withdrawal of consent, whichever occurs first. Subjects who discontinue study drug without progressive disease (PD) will continue to undergo tumor assessments every 6 weeks until documented PD or initiation of another anticancer therapy.

The data cutoff for the primary analysis will occur once the last subject completes 6 cycles of investigational therapy. Subjects will be allowed to continue treatment until progression or the end of therapeutic benefit from the study drug as determined by Sponsor discussion with investigator.

The end of study is defined as when the last ongoing subject completes their off treatment visit. The off treatment visit should occur 30 days after final dose with a window of ± 3 days. The maximum estimated period for each subject on treatment is anticipated to be approximately 4 months. However, subjects may continue to receive study treatment, as long as they demonstrate clinical benefit as judged by the investigator after discussion with the Sponsor or until the end of the study.

Number of Subjects

Approximately 30 to 128 subjects are planned to be enrolled in this study: 30 to 48 during the Dose Escalation phase and 40 to 80 subjects in the Dose Expansion phase. The total number of subjects to be enrolled in the Dose Escalation phase is dependent upon the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD and/or RP2D of H3B-6527.

Inclusion Criteria

In order to be eligible for participation in this study, subjects must:

1. Be ≥18 years of age.
2. Have an Eastern Cooperative Oncology Group Performance Status of 0 or 1.
3. Have an HCC diagnosis with the following criteria:
    - Confirmed by available pathology records or current biopsy (confirmed diagnosis may be made by histological examination or by noninvasive criteria according to the European Association for the Study of the Liver or the American Association for the Study of Liver Disease Guidelines)
    - Advanced, unresectable, or recurrent
    - Progressing since the last antitumor therapy
    - Child-Pugh A classification
    - No clinically significant ascites
    - Must have received at least one prior standard-of-care therapy, unless contraindicated.
4. Must be FGF19-positive, as determined by a Sponsor-designated laboratory from a fresh tumor sample prior to enrollment in the Dose Expansion phase.
5. Have completed any prior chemotherapy, monoclonal antibody or immunotherapy (eg, tumor vaccine, cytokine, or growth factor given to control the cancer) at least 4 weeks or 5 half-lives (whichever is shorter) before study drug administration, and all AEs must have either returned to baseline or resolved to Grade 0 or 1.

6. Have completed any prior definitive radiation therapy at least 3 weeks before study drug administration; any prior focal radiotherapy at least 2 weeks before study drug administration; irradiated lesions should show evidence of size increase as defined in inclusion criterion #7 if they are intended to be followed as target lesions. Radiopharmaceutical therapy (strontium, samarium, and yttrium) must have been completed 8 weeks before study drug administration.
7. Have tumor tissue available as follows:
    a. Part 1, Dose Escalation: Tumor tissue (screening acquisition or archival tissue if obtained) is requested but not mandated.
    b. Part 2, Dose Expansion: Fresh tumor tissue must be available (collected up to 8 weeks before administration of H3B-6527 on C1 Day 1). Archival tissue if available is requested but not mandated.
8. Have measurable disease as follows:
    a. Part 1, Dose Escalation: Subjects may have measurable or nonmeasurable disease as defined by mRECIST.
    b. Part 2, Expansion: Subjects must have measurable disease meeting the following criteria:
        i. Subjects with HCC: At least 1 measurable target lesion according to mRECIST that meets the following criteria:

- Hepatic lesion
    - The lesion can be accurately measured in at least one dimension as ≥1.0 cm
    - The lesion is suitable for repeat measurement
    - The lesion shows intratumoral arterial phase enhancement on contrast-enhanced CT or MRI
- Nonhepatic lesion
    - Lymph node lesion that measures at least one dimension as ≥1.5 cm in the short axis, except for porta hepatis lymph node that measures ≥2.0 cm in the short axis
    - Non-nodal lesion that measures ≥1.0 cm in the longest diameter

Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression by mRECIST to be deemed a target lesion.

9. Have left ventricular ejection fraction >50% on echocardiography or multiple-gate acquisition (MUGA) scan.
10. Have adequate renal function defined as serum creatinine <1.5 ×upper limit of normal (ULN; or calculated creatinine clearance ≥50 mL/min per the Cockcroft and Gault formula).
11. Have adequate bone marrow function as follows:
    a. Absolute neutrophil count ≥1500/mm^3 (≥1.5×10^9/L)
    b. Platelet counts ≥75,000/mm^3 (≥75×10^9/L)
    c. Hemoglobin ≥9.0 g/dL (may have been transfused).
12. Have adequate liver function as follows:
    a. Adequate blood coagulation as evidenced by an International Normalized Ratio ≤1.5.

b. Total bilirubin ≤1.5 ×ULN.

c. Alanine aminotransferase and aspartate aminotransferase ≤5 ×ULN.

d. No evidence of biliary duct obstruction unless obstruction controlled by local treatment or, the biliary tree can be decompressed by endoscopic or percutaneous stenting with subsequent reduction in bilirubin to ≤1.5 ×ULN.

13. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

    NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing).

14. Females of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment and for at least 1 month after finishing treatment. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (eg, sexual abstinence, an intrauterine device, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation. Women using oral hormonal contraceptives should add a barrier method.

15. Be willing and able to comply with all aspects of the protocol.

16. Provide written informed consent prior to any study-specific screening procedures.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Other malignancy active within the previous 2 years except for basal or squamous cell skin cancer, stage 1 prostate cancer, superficial bladder cancer or carcinoma in situ of the cervix or breast that has completed curative therapy.

2. Current evidence of corneal disorder/keratopathy including but not limited to corneal epithelial thinning, bullous/band keratopathy, corneal abrasion, inflammation/ulceration, or keratoconjunctivitis (to be confirmed by ophthalmological examination). Pre-existing cataract is not a reason for exclusion.

3. Brain or subdural metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting

treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.

4. Genetic diseases of the liver that may complicate review of safety data.
5. Known human immunodeficiency virus infection.
6. Uncontrolled significant active infections, except hepatitis B virus (HBV) or hepatitis C virus (HCV). Subjects with HBV are eligible but should be taking an appropriate antiviral medication if indicated. Subjects with HCV are eligible but must not be taking concomitant treatment for HCV while receiving H3B-6527.
7. Major surgery or other locoregional treatment within 4 weeks before the first dose of study drug or radionuclide treatment (eg, ^{90}Yttrium intra-arterial treatment) 8 weeks before study drug administration.
8. Inability to take oral medication, or presence of a malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) that might impair the bioavailability of H3B-6527. Subjects with prior gastric resection are eligible.
9. Use of any drug that is a strong inhibitor or inducer of the cytochrome P450 (CYP) CYP3A4 enzyme or the P-glycoprotein transporter within at least 2 weeks before the start of study drug and during the conduct of the study unless there is an emergent or life-threatening medical condition that requires it.
10. Use of any drug known to prolong corrected QT (QTc) interval within at least 2 weeks before the start of the study drug and during the conduct of the study.
11. Treatment with proton pump inhibitors that cannot be discontinued 3 days prior to the start of study drug and during the course of the study; antacids are permitted except for calcium carbonate antacids (eg, Tums®).
12. Use of other investigational drugs within 28 days or at least 5 half-lives (whichever is shorter) before study drug administration.
13. Previous treatment with a selective FGF19-FGFR4 targeted therapy.
14. Use of any live vaccines against infectious diseases (eg, influenza, varicella) within 4 weeks (28 days) of initiation of study therapy.
15. Presence of gastric or esophageal varices requiring active treatment.
16. A clinically significant electrocardiogram (ECG) abnormality, including a marked baseline prolonged QTc interval (eg, a repeated demonstration of a QTc interval >450 ms).
17. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug; or cardiac arrhythmia requiring medical treatment (including oral anticoagulation).
18. Any other major illness, medical condition or concomitant medication that, in the investigator's judgment, will substantially increase the risk associated with the subject's participation in this study or would compromise the subject's ability to safely complete the study.
19. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 90 days after study drug

discontinuation). No sperm donation is allowed during the study period or for 90 days after study drug discontinuation.

20. Hypersensitivity to the study drug or to any of the excipients.
21. Intolerance or hypersensitivity to both CT and MRI contrast material that would preclude the ability to acquire the triphasic liver imaging required by the protocol.
22. An inorganic phosphorus > ULN for the institution. Note: Subjects may be on treatment for hyperphosphatemia, but the levels must be normal at screening to participate in this study. Subjects with high levels on screening may subsequently be treated and rescreened and, should they have stable levels for 2 weeks prior to study, may enter the study.
23. A total or ionized serum calcium > ULN for the institution. Note: Subjects may be on treatment for hypercalcemia, but the levels must be normal at screening to participate in this study. Subjects with high levels on screening may subsequently be treated and rescreened and, should they have stable levels for 2 weeks prior to study, may enter the study.
24. Endocrine changes that may result in increases in calcium or phosphate, including but not limited to hyperparathyroidism and tumoral calcinosis.
25. Past medical history and/or current evidence of tumoral calcinosis or tissue calcification.
26. Use of calcium or vitamin D supplements or systemic corticosteroids. The duration between the last systemic corticosteroid administration and the first dose of study drug should be at least 2 weeks.
27. Hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption.

Study Treatment

Test drug: H3B-6527 will be supplied as 50-, 100-, and 200-mg capsules. The starting dose will be 300 mg QD orally, with escalation of total daily doses in successive cohorts to a maximum planned dose of 2000 mg. Additionally, a BID dosing schedule may be explored. In this case, the initial total daily dose given BID will be equal to a total daily dose that has been well tolerated as a QD dose.

The study drug will be administered with food based on the Healthy Volunteers Food-Effect study (Study H3B 6527-A001-001: A Randomized Phase 1 Food-Effect Study of H3B-6527 in Healthy Subjects).

Capsules should be swallowed whole. Dosing should not be repeated if a subject vomits. For subjects on a QD dose schedule, a dose missed by >8 hours should be skipped. For subjects on a BID dose schedule, a dose missed by >4 hours should be skipped.

Guidelines for Continuation of Treatment

Study drug should continue to be administered until disease progression, development of unacceptable toxicity, withdrawal of consent, or termination of the study by the Sponsor.

Subjects who experience a DLT during C1, will be discontinued from treatment. In rare cases, an exemption to study discontinuation for a DLT in C1 may be considered after discussion between the treating physician, Sponsor and study medical monitor.

If a subject experiences a DLT or dose-modifying event (ie, an AE meeting the criteria for a DLT but occurring after C1) during the study then study treatment will be interrupted and subjects may, at the discretion of the investigator, and after discussion with the Sponsor, be allowed to continue study drug at a reduced dose, if the following criteria are met:

- Absolute neutrophil count $\geq 1.0 \times 10^9$/L (1,000/mm^3)
- Platelet count $\geq 75 \times 10^9$/L (75,000/mm^3)

- All other nonhematologic treatment-related toxicities are Grade 0 or 1 (except alopecia) or return to baseline level
- The subject is deriving clinical benefit, and
- The subject has an otherwise favorable risk/benefit profile.

The magnitude of the dose reduction cannot be specified a priori since the actual doses evaluated and the dose-toxicity relationship will not be known until there is clinical experience with H3B-6527; however, a minimum reduction of 33% must be taken. The dose chosen will require discussion and agreement between the investigator and Sponsor following review of the relevant clinical data.

Dose reductions are allowed for all subjects. However, once the H3B-6527 dose has been reduced for a given subject, no re-escalation will be permitted for that subject.

A maximum of 2 dose reductions will be allowed as needed but study treatment should not be resumed in the case of the following treatment-related events:

- Occurrence of a DLT in C1 except upon agreement with investigator, Sponsor and medical monitor. A dose reduction must be taken if treatment is resumed.
- CTCAE Grade 3 or 4 cardiac event
- Nonhematologic events of Grade 4 severity
- Dose delay of ≥21 days for a treatment-related event in C2 and beyond.

Comparator Drug: None

Duration of Treatment

In the Dose Escalation and Dose Expansion phases of the study, each subject will receive 1 cycle of treatment during the Treatment Phase. In the Extension Phase, study treatment will continue until the subject develops PD or unacceptable toxicity or withdraws consent, or until termination of the study by the Sponsor. However, subjects may continue to receive study treatment, as long as clinical benefit is demonstrated, as judged by the investigator after discussion with the Sponsor or until the end of the study.

Concomitant Drug/Therapy

The following are prohibited:

- Other investigational drugs.
- Other antitumor therapies such as chemotherapy, surgical resection, or antitumor immunotherapy.
- Proton pump inhibitors.
- Radiotherapy for central metastases (eg, vertebral, mediastinal) will not be allowed; the need for such radiotherapy while on study will be seen as an indication of disease progression and the subject should be withdrawn from therapy. However, palliative radiotherapy for up to 2 local peripheral metastases not being used as target lesions is allowed but the need for such therapy may be an indication of PD and should be discussed with the Sponsor prior to implementation.
- Drugs that are strong inhibitors or inducers of CYP3A4 enzyme or P-glycoprotein transporter.
- Drugs that raise serum calcium and phosphorus levels (eg, vitamin D supplements, calcium dietary supplements, calcium antacids) or systemic corticosteroids. The duration between the last systemic corticosteroid administration and the first dose of study drug should be at least 2 weeks. If a short-term course of systemic corticosteroids is required while on treatment, then study drug must be held while the subject receives systemic corticosteroid treatment. If the subject has not progressed in the interim, resumption of treatment with H3B-6527 may be considered following discontinuation of steroid treatment and a 2-week washout period.

Growth Factors: Subjects receiving recombinant erythropoietin or darbepoietin-α prior to study start may continue to receive pretreatment doses. Following initiation of study treatment, the use of erythropoietic and granulocyte growth factors in accordance with local practice or guidelines. American Society for Clinical Oncology guidelines may be implemented at the discretion of the treating physician.

Management of diarrhea: Subjects should be instructed to take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. During the night, subjects may take 4 mg of loperamide every 4 hours. Subjects should be advised to avoid dehydration through adequate fluid intake. Bile acid sequestrants may be utilized in the case of bile acid diarrhea.

Medications for the treatment of AEs or cancer symptoms, eg, packed red blood cells and pain medications, are allowed. Additionally, medications (not addressed above) used to treat underlying medical conditions at study entry including anti-emetics and antidiarrheals will be allowed to continue.

Guidelines for Management of Hyperphosphatemia or Hypercalcemia

Phosphorus and calcium will be measured at screening, before the first dose, every week with safety labs during C1, and on Day 1 and Day 8 for C2 and beyond. Please note that a cycle is 21 days. Subjects with elevated levels of phosphorus or calcium at screening, as defined as being >1 ×ULN on local laboratory ranges, may not participate in this study and should be referred for management of such. If successfully controlled, subjects may be rescreened. During study participation, any levels of phosphorus above 7 mg/dL, or calcium equal to or above Grade 2 hypercalcemia as per CTCAE, Version 4.03, will result in the dose of H3B-6527 being held for 14 days.

The hyperphosphatemia and / or hypercalcemia should be managed by local practice, with medication, diet change, and potential referral as necessary. After 14 days of holding the drug, if the phosphorus level has returned to 5.5 mg/dL or lower, and the calcium is less than or equal to a Grade 1 elevation, the subject may begin taking H3B-6527 again at one dose level lower than their original dose and should continue other measures initiated during the drug holiday, such as phosphorus lowering agents, while on study. If a subject should experience hyperphosphatemia above 7 mg/dL or hypercalcemia equal to or above Grade 2 again on study, then study therapy will be discontinued.

Assessments

Efficacy Assessments

Tumor assessments will be performed following mRECIST guidance.

All subjects are required to undergo chest, abdomen, and pelvis imaging at baseline and all follow-up time points. Contrast-enhanced CT scan of the chest and contrast-enhanced CT or MRI scan of the abdomen, pelvis, and any other areas of disease, as clinically indicated, will be acquired at Screening and at all imaging time points. A liver CT or MRI scan must be performed using triphasic scanning techniques optimized to capture precontrast, arterial, and portal venous phases. Historical standard-of-care scans conducted within 28 days prior to study drug administration may be used as screening/baseline imaging if scanning parameters are consistent with the requirements for this protocol as separately defined by the imaging core laboratory.

MRI scans may be used instead of CT scans for imaging of the abdomen and pelvis. However, the chest must be imaged using CT; and chest disease must be followed by CT scan (ie, chest x-ray for response assessment is not allowed). The same method of assessment used during Screening must be used at all subsequent time points. If iodinated intravenous contrast is contraindicated, chest CT scan should be performed without intravenous contrast.

A brain scan should be performed for all subjects to assess potential central nervous system disease and/or metastases as clinically indicated. For eligible subjects with previously treated brain metastases, a brain scan will be required at all tumor assessment time points (eg, every 6 weeks). For all subjects, a follow-up brain scan must be performed to confirm a complete response (CR) within 1 week following response confirmation.

The first radiological assessment of tumor response status will be performed during Week 6, unless there is clinical indication warranting earlier radiologic imaging. Response assessments will be repeated every 6 weeks until disease progression as determined by the investigator. Although clinical progression may be determined by the investigator based upon clinical deterioration, every effort should be made to document progression using radiographic methods. Signs and symptoms of clinical deterioration that lead to disease progression should be documented.

Subjects discontinued from treatment without disease progression will continue to undergo tumor assessments every 6 weeks until documented disease progression or initiation of another anticancer therapy.

Subjects who discontinue study treatment, regardless of their reasons for doing so, will be followed for survival approximately every 12 weeks for up to 12 months or until 6 cycles after last patient in, death, loss to follow-up, or withdrawal of consent, whichever occurs first.

Pharmacokinetic Assessments

Plasma samples for PK analyses will be collected during C1 on Day 1, Day 8, and Day 15 in Part 1, Dose Escalation. Plasma samples for PK analyses will be collected during C1 on Day 8, and Day 15 in Part 2, Expansion, according to the Schedule of Assessments.

Urine and plasma samples for assessment of the metabolite profile will be collected during C1 on Day 8 for urine and Day 1, Day 8, and Day 15 for plasma in Part 1, Dose Escalation, only.

During the Expansion phase, H3B-6527 levels in tumor tissue may be analyzed. During Dose Escalation, the investigators and Sponsor may agree that determination of H3B-6527 exposure in tumor tissue is required to guide decisions pertaining to drug administration. In this scenario, biopsies of tumor tissue will be obtained from all consenting subjects.

Pharmacodynamics, Pharmacogenomics, and Other Biomarker Assessments

Pharmacodynamics biomarkers including biomarkers to show target engagement and impact of H3B-6527 treatment on disease will be evaluated from collected samples as outlined in the schedule of assessments. Retrospective testing for potential subject stratification markers will also be explored. Results from biomarker studies may be used to aid the selection of the RP2D and schedule, and for monitoring drug efficacy. When new research results emerge, the parameters and methods for the pharmacodynamic biomarker analysis may change.

Biomarker Sample Collection

Screening Phase biomarkers:

Subjects in the Dose Expansion phase will be evaluated for FGF19 expression. A fresh tumor biopsy (for determining FGF19 expression levels by a Sponsor designated laboratory), the signing of the ICF, and the collection of blood samples for pharmacodynamic analysis (same day as fresh tumor biopsy) will be required up to 8 weeks before administration of H3B-6527 on C1 Day 1, in order to enroll in the Dose Expansion Phase of the study. The 28-day Screening Period will begin when any of the remaining screening assessments are performed. The entire Pretreatment Phase must be completed within 8 weeks of study drug administration on C1 Day 1. Archived, fixed tumor tissue is also to be collected (if available) for all consenting subjects in both the Dose Escalation and Expansion phases. These tissues and peripheral blood samples (for both Dose Escalation and Dose Expansion phase) may be used for assessment of mutations and other exploratory biomarkers.

Baseline and Treatment Phase Biomarkers:

Blood (serum/plasma) biomarker samples from study subjects may be analyzed for FGF19 (ligand of H3B-6527's target FGFR4), bile acids, circulating tumor cells and other exploratory biomarker candidates (both protein and nucleic acids) using global proteomic/metabolomics/genomic methods, enzyme-linked immunosorbent assay, multiplex bead-based immunoassay, or other assays/methods. These blood biomarker samples may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes as well as for potential use in diagnostic development.

In the event a subject is required to have a repeat tumor biopsy for medically indicated reasons, freshly obtained biopsy tissue from the procedure should be collected and shipped to H3 Biomedicine, Inc., or a predesignated laboratory for exploratory biomarker analysis as outlined in the laboratory manual.

Pharmacogenomics Assessment

A blood sample will be collected for pharmacogenomic (PG) analysis. The role of deoxyribonucleic acid (DNA) sequence variability on the absorption, distribution, metabolism, and elimination (ADME) of H3B-6527 may be evaluated in this study. Variation in H3B-6527 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or pharmacodynamic data. Genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor.

Data obtained will be used for research, to assist in developing safer and more effective treatments, and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The

DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, ribonucleic acid, and protein) may be stored for up to 15 years to assist in any research scientific questions related to H3B-6527 or cancer and for potential diagnostic development.

General

Archived tumor tissue samples and blood samples for pharmacodynamic, PG, and other biomarker assessments will be collected from all consented study subjects, except where prohibited by regional or local laws. Samples will be collected at designated time points as specified in the Schedule of Procedures/Assessments.

Samples may be used for biomarker discovery and/or validation to identify blood or tumor biomarkers that may be useful to predict treatment response (efficacy, pharmacodynamics), PK, and/or safety-related outcomes. Samples may also be used for potential diagnostic development. In addition, biomarkers identified in other clinical studies may also be assessed in samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis will be based on the clinical outcome of the study, the signals observed in other clinical studies and/or the scientific rationale of the study.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Safety Assessments

Safety assessments include monitoring and recording all AEs, including serious adverse events (SAEs); clinical laboratory tests (including hematology, coagulation parameters, clinical chemistry (including total bile acids, cholesterol, triglycerides), and urinalysis; and periodic measurement of vital signs, ECGs, MUGA scans/echocardiograms, ophthalmic and physical examinations. Additionally, QTc intervals will be evaluated during Dose-Escalation. All AEs will be assessed using the National Cancer Institute CTCAE, Version 4.03.

Bioanalytical Methods

Plasma concentrations of H3B-6527 will be determined using a validated assay. If appropriate, assessment of plasma and urine samples for any metabolites of H3B-6527 may be explored.

The ability to determine tumor concentrations of H3B-6527 may be explored using a nonvalidated assay such as matrix-assisted laser desorption/ionization.

Statistical Methods

Primary Endpoints

- Occurrence of DLTs as a function of the dose of H3B-6527 for determination of the MTD and RP2D.
- Safety/tolerability: the type and frequency of AEs, SAEs using CTCAE, Version 4.03, as well as changes in clinical laboratory values, ECG parameters and vital sign measurements.

Secondary Endpoints

- PK: Standard primary PK parameters including but not limited to the area under the plasma concentration-time curve from time 0 through the last measurable point (AUC_{0-t}), maximum observed plasma concentration (C_{max}) and time of maximum observed plasma concentration (t_{max}).

- Preliminary antitumor activity: Response will be determined by the investigator using mRECIST. The following endpoints will be determined:
  - Objective response rate (ORR), defined as the proportion of subjects achieving a best overall response of partial response (PR) or CR (PR + CR), from first dose date until disease progression/recurrence.
  - Duration of response, defined as the time from the date of first documented CR/PR until the first documentation of disease progression as determined by the investigator or death, whichever comes first.
  - Progression-free survival (PFS), defined as the time from first dose date to the date of the first documentation of disease progression as determined by the investigator or death (whichever occurs first).
  - Overall survival (OS), defined as the time from first dose date to the date of death.
  - Time to response, defined as the time from first dose date to the date of first documented CR/PR.

Exploratory Endpoints

- Correlation of biomarker expression levels with antitumor activity and safety
- Expression levels of biomarkers in blood and tumor samples
- Correlation of biomarker expression levels with H3B-6527 exposure in plasma
- H3B-6527 levels in tumor tissue may be assessed
- H3B-6527 metabolites in plasma and urine.

Analysis Sets

Full Analysis Set will include all subjects who received at least 1 dose of study drug. This will be the primary analysis set for efficacy evaluations, as well as for demographic and baseline characteristics. The summary of efficacy will be based on this set for HCC subjects.

Safety Analysis Set will include all subjects who received at least 1 dose of the study drug. This will be the analysis set for all safety evaluations except DLT results.

PK Analysis Set will include all subjects who have received at least 1 dose of study drug and have at least 1 evaluable plasma concentrations.

Pharmacodynamics Analysis Set will include all subjects who have received at least 1 dose of study drug and have evaluable pharmacodynamic data.

PK/Pharmacodynamics Analysis Set will consist of all subjects in the Safety Analysis Set that also have evaluable plasma PK and pharmacodynamic pretreatment assessment and at least 1 post treatment assessment.

Response Evaluable Set will consist of those HCC subjects who have received at least 1 dose of study drug and have measurable disease at baseline and at least 1 postbaseline evaluation.

Efficacy Analyses

ORR, response duration, time to response, PFS, and OS will be listed and descriptively summarized as appropriate.

- **Response duration and time to response:** Summary statistics (median Q1, Q3 and range)

will be generated on subjects achieving a best overall response of PR or CR (PR + CR).

PFS and OS: The PFS censoring rules will follow the Food and Drug Administration guidance. PFS will be reported in both summary tables and plotted with Kaplan-Meier curve. Time of death will be censored for subjects who are without death information at the time of OS analysis. OS will be reported in both summary tables and plotted with Kaplan-Meier curve.

Pharmacokinetic Analyses

Plasma concentrations of H3B-6527 will be tabulated and summarized by dose level, day, and time. H3B-6527 PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: C_{max}, t_{max}, AUC_{0-t}, accumulation ratio (R_{acc}); and if data permit, area under the plasma concentration-time curve extrapolated to infinity (AUC_{0-inf}), terminal elimination half-life ($t_{½}$), apparent total body clearance (CL/F), and apparent volume of distribution during the terminal phase (V_z/F).

Pharmacodynamics, Pharmacogenomics, and Other Biomarker Analyses

Pharmacodynamics, PG and other biomarker analyses may be performed and reported separately. Details of these analyses will be described in a separate analysis plan.

Safety Analyses

Evaluation of safety will be performed on the Safety Analysis Set. Safety data to be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and the results of ophthalmic and physical examinations.

Safety parameters will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, and range for continuous variables; numbers and percentages for categorical measures).

The effects of H3B-6527 on cardiovascular repolarization will be evaluated via 12-lead continuous Holter/ECG monitoring on C1 Day 1 and Day 8 in the Dose Escalation phase of the study only. Individual ECGs will be extracted from the Holter recordings at specified time points per ECG manual and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for heart rate using Fridericia's formula (QTcF) correction factor. The primary QTc parameter will be QTcF. Secondary parameters (QT corrected for heart rate using Bazett's formula [QTcB], QT, PR, QRS, and heart rate) and waveforms (T waves) will be evaluated.

Interim Analyses

There is no formal interim analysis for efficacy. There will be an interim analysis to define the MTD and/or RP2D prior to initiating the Expansion phase of the study. Other interim analyses may be performed to determine if a different dose schedule (eg, BID) or frequency (eg, 2 weeks on/1-week off) may be preferable. Safety and PK summaries may be provided periodically.

Sample Size Rationale

Dose Escalation phase (Part 1)

It is anticipated that selection of the RP2D will be based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data. The total number of subjects to be enrolled is dependent upon the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD of H3B-6527 and establish the RP2D. For each dose schedule of QD and BID, assuming 5 dose levels for QD dose schedule and 3 dose levels for the BID dose

schedule will be studied and a maximum of 6 subjects will be enrolled per dose level, then between 30 to 48 subjects may be accrued during dose escalation.

Dose Expansion phase (Part 2)

Prior to starting the Dose Expansion phase, the investigators and the Sponsor will use safety, efficacy, PK, and pharmacodynamic data obtained during the Dose Escalation Phase, as well as clinical judgement, to jointly determine the dose schedules to be studied.

During Part 2, the Dose Expansion phase, a sample size of 40 evaluable subjects per dose schedule will be enrolled to examine QD and/or BID dosing of H3B-6527 based on the recommended dose determined from Part 1. For a reference of the precision of ORR estimates, the associated 2-sided 95% CIs for ORR up to 30% for 40 subjects are provided. This study makes provision for exploring a BID schedule of H3B-6527 during the Dose Expansion phase if evaluation of the PK, pharmacodynamics, or safety of H3B-6527 suggests that it may be preferable to administer H3B-6527 BID rather than QD. When both dose schedules are accruing subjects, an alternating enrollment schema into QD and BID dose schedules will be followed.

Treatment Arms for Part 2, Dose Expansion

Treatment Arm	Number of Subjects
1: Subjects with advanced HCC who are FGF19-positive to receive H3B-6527 QD for 21-day cycles	40 subjects
2: Subjects with advanced HCC who are FGF19-positive to receive H3B-6527 BID for 21-day cycles	40 subjects

BID = twice daily, HCC = hepatocellular carcinoma.

2-sided 95% Confidence Interval for ORR Estimate Up to 30% (40 subjects)

ORR (N=40)	2-sided 95% CI
5% (2 responders in 40 subjects)	(0.006, 0.169)
7.5% (3 responders in 40 subjects)	(0.016, 0.204)
10% (4 responders in 40 subjects)	(0.028, 0.234)
12.5% (5 responders in 40 subjects)	(0.042, 0.268)
15% (6 responders in 40 subjects)	(0.057, 0.298)
17.5% (7 responders in 40 subjects)	(0.073, 0.328)
20% (8 responders in 40 subjects)	(0.091, 0.356)
22.5% (9 responders in 40 subjects)	(0.108, 0.385)
25% (10 responders in 40 subjects)	(0.127, 0.412)
27.5% (11 responders in 40 subjects)	(0.146, 0.439)
30% (12 responders in 40 subjects)	(0.166, 0.465)

CI = confidence interval, ORR = objective response rate.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ß-hCG	beta-human chorionic gonadotropin
ADME	absorption, distribution, metabolism, and elimination
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{0\text{-inf}}$	area under the plasma concentration-time curve extrapolated to infinity
$AUC_{0\text{–t}}$	area under the plasma concentration-time curve from time 0 through the last measurable point
BID	twice daily
BP	blood pressure
C	cycle
CA	Competent Authority
CFR	Code of Federal Regulations
CL/F	apparent total body clearance
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum observed plasma concentration
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose-limiting toxicity
DME	dose-modifying events
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EU	European Union
FDA	Food and Drug Administration

Abbreviation	Term
FGF19	fibroblast growth factor 19
FGFR	fibroblast growth factor receptor
FGFR4	fibroblast growth factor receptor 4
GCP	Good Clinical Practice
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HED	human equivalent dose
HNSTD	highest non-severely toxic dose
HR	heart rate
HU	Hounsfield units
ICF	informed consent form
ICH	International Council for Harmonisation
ID	identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
mRECIST	Modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multiple-gate acquisition
NE	not evaluable
OCT	optical coherence tomography
ORR	objective response rate
OS	overall survival
OTV	off-treatment visit
PD	progressive disease
PFS	progression-free survival
PG	pharmacogenomics
PI	principal investigator
PK	pharmacokinetic(s)
PO	by mouth

Abbreviation	Term
PR	partial response
PT	preferred term
QD	once daily
QTc	corrected QT
QTcF	QT corrected for heart rate using Fridericia's formula
QTcB	QT corrected for heart rate using Bazett's formula
R_{acc}	accumulation ratio
RP2D	Recommended Phase 2 dose
RR	respiratory rate
SAE	serious adverse event
SD	stable disease
SI	Système International
SOC	system organ class
SOD	sum of diameters
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time of maximum observed plasma concentration
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
V_z/F	apparent volume of distribution during the terminal phase
WHO	World Health Organization

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the Sponsor.

A signed letter of study approval (or an electronic approval) from the IRB/IEC chairman must be sent to the principal investigator (PI) with a copy to the Sponsor before study start and the release of any study drug to the site by the Sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator will immediately send the notice of study suspension or termination by the IRB/IEC to the Sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or Sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the Sponsor at the time of each periodic report. The investigator(s) or the Sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the Sponsor (or designee) should notify the IRB/IEC and Competent Authority (CA) within 90 days if required. The end of the study will be the date of the last study visit for the last subject in the study. The Sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the Sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (64th WMA General Assembly, Fortalenza Brazil, October 2013)

- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the CAs of all involved EU member states.
- Other applicable regulatory authorities' requirements or directives.

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject (or guardian/legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF up to 8 weeks before the first dose of study drug. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations (ie, Title 21 CFR Part 50). Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the Sponsor and kept on file according to local procedures at the site.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of H3 Biomedicine, Inc. (H3B; the Sponsor), a wholly owned subsidiary of Eisai Co, Ltd. in the United States (US) and under the sponsorship of Eisai Co, Ltd. outside the US. A total of approximately 40 investigational site(s) will be activated globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the Sponsor and of the contract research organization(s) (CRO[s]) are listed in the Study Operations Manual provided to each site.

7 INTRODUCTION

Liver cancer is the second leading cause of cancer-mortality and the 16th absolute cause of death worldwide (GBD 2013 Mortality and Causes of Death Collaborators, 2015). The high incidence and poor prognosis associated with advanced hepatocellular carcinoma (HCC) together with the lack of effective systemic therapies warrant the development of new therapies for this indication (Llovet, et al., 2008). Although there are many studies ongoing, sorafenib, a multi-receptor kinase inhibitor, currently is considered the standard of care for unresectable HCC in the US, the EU, and multiple countries in the rest of the world (Nexavar® US Prescribing Information [USPI], 2015).

H3B-6527 is an oral, selective, and covalent small molecule inhibitor of fibroblast growth factor receptor 4 (FGFR4). In vitro, H3B-6527 showed >250-fold selectivity towards FGFR4 compared to other kinases tested. FGFR4 and its major activator fibroblast growth factor 19 (FGF19), play a critical role in HCC. Addition of H3B-6527 to FGF19-overexpressing HCC cell lines leads to dose-dependent inhibition of FGF19/FGFR4 signaling and concomitant reduction in the viability of cells. H3B-6527 dosing in mice leads to inhibition of FGF19/FGFR4 signaling and tumor regression in FGF19-overexpressing HCC cell line-derived xenografts and HCC patient-derived xenografts.

These genetic analyses along with preclinical findings support the investigation of H3B-6527 in patients with advanced HCC.

This first-in-human study is an open-label, multicenter, Phase 1, dose-finding study that will be conducted in 2 parts: a Dose Escalation Phase and a Dose Expansion phase. The primary objectives are to determine the maximum tolerated dose (MTD) of H3B-6527 and to assess the safety and tolerability of H3B-6527 as a single agent in subjects with advanced HCC.

7.1 Indication

Liver cancers occur predominantly in developing regions, most commonly in China, with 83% of the estimated 782,000 new cancer cases worldwide occurring in developing regions in 2012, according to the World Health Organization (WHO). Liver cancers are more common in men than in women, ranking as the fifth most common cancer among men and ninth among women. Globally, liver cancer is the second most common cause of cancer

deaths, estimated to be responsible for approximately 746,000 deaths in 2012 (9.1% of the total). Whereas mortality rates have decreased over the past several decades in many cancer types, the mortality rates for liver cancers, including bile duct cancers, have doubled over that same time period (Llovet, et al., 2015).

The most common type of primary liver cancer is HCC, accounting for up to 90% of all primary liver cancers worldwide (Llovet, et al., 2015). The main risk factors for liver cancer are hepatitis B virus (HBV), hepatitis C virus (HCV), and chronic hepatitis and cirrhosis secondary to alcohol use and other causes, with HBV and HCV being the most common causes (GBD 2013 Mortality and Causes of Death Collaborators, 2015).

Most patients with liver cancers are diagnosed at intermediate or advanced disease stages, where curative approaches are often not feasible (Llovet, et al., 2015). For patients with advanced disease, treatment options are limited. Thus, the prognosis for those with advanced disease is poor.

The molecular targeted agent sorafenib, a multireceptor kinase inhibitor, currently is considered the standard of care for unresectable HCC in the US, EU, and multiple countries in the rest of the world (Nexavar USPI, 2015). In a Phase 3, double-blind, randomized, placebo-controlled clinical study in patients with unresectable HCC, sorafenib was associated with significant prolongation of survival versus placebo (median survival 10.7 versus 7.9 months, respectively; $P<0.001$) as well as significant prolongation of time to progression (5.5 versus 2.8 months, respectively; $P<0.001$) (Nexavar USPI, 2015). However, in clinical practice, sorafenib demonstrates only modest efficacy and is associated with toxicity in patients with HCC (Cheng, et al., 2012).

Enhanced fibroblast growth factor receptor (FGFR) expression is commonly observed in various types of human malignancies (Tiong, et al., 2013). Signaling through the fibroblast growth factor family is involved in fibrosis and its progression to cirrhosis of the liver, which is a risk factor for the development of HCC. Several alterations in FGFR signaling correlate with the outcomes of HCC patients, suggesting that signaling through this family of proteins contributes to the development or progression of HCC tumors (Cheng, et al., 2012). The main FGFRs expressed in liver tissues are FGFR3 and FGFR4 (Cheng, et al., 2012).

Recent genomic studies have identified FGF19 as a driver oncogene in HCC. FGF19 is a gut-secreted hormone that acts in the liver through FGFR4 to regulate bile acid synthesis. Consistent with the notion that FGF19 is a driver oncogene in HCC, transgenic mice overexpressing FGF19 form liver tumors and genetic ablation of FGFR4 prevented tumor formation. These data suggest that targeting HCC, which is dependent on FGFR4 signaling, would have therapeutic benefit in patients with altered FGF19 signaling, although tumor regression has also been observed in patient-derived xenograft models of HCC with undetectable levels of FGF19. While a number of pan-FGFR inhibitors are being clinically evaluated, their application to FGFR4-dependent HCC may be limited by their FGFR1-3-related dose-limiting toxicities (DLTs).

7.1.1 H3B-6527

7.1.1.1 Therapeutic Pathway

H3B-6527 is a selective FGFR4 inhibitor being developed for the treatment of FGF19/FGFR4-driven HCC. Biochemical selectivity assays showed that H3B-6527 is >250-fold more selective towards FGFR4 compared to other kinases tested. The addition of H3B-6527 to FGF19-amplified HCC cell lines led to dose-dependent inhibition of FGF19/FGFR4 signaling and concomitant reduction in the viability of cells. Importantly, these effects were only observed in FGF19-altered HCC cell line models.

H3B-6527 dosing in mice leads to pharmacodynamic modulation and tumor regression in FGF19-altered HCC cell line-derived xenografts. In addition, ongoing preclinical studies in HCC patient-derived xenograft mouse models showed that both FGF19-altered (detectable) and FGF19-unaltered (undetectable) models respond to H3B-6527. In particular, significant tumor growth inhibition relative to vehicle control was seen with H3B-6527 at oral doses of 100 and 300 mg/kg twice daily (BID) in the HEP3B xenograft model and at oral doses of 300 mg/kg and 500 mg/kg BID in the JHH7 model.

Genetic analyses along with nonclinical study findings support the investigation of H3B-6527 in patients with advanced HCC.

7.1.1.2 Clinical Experience with H3B-6527

The current study represents the first clinical investigation of H3B-6527.

7.1.1.3 Common Serious Adverse Events Expected to Occur in the Study Population in the Absence of Study Drug Exposure

Common serious adverse events (SAEs) expected to occur in this study population include hepatobiliary dysfunction, ascites, gastrointestinal hemorrhage, fatigue, abdominal pain and renal failure. The current study represents the first clinical investigation of H3B-6527; therefore, the clinical safety profile of this investigational agent is unknown. Based on nonclinical studies, AEs potentially associated with H3B-6527 may include corneal atrophy, hepatocellular hypertrophy, hepatobiliary toxicity, gastrointestinal toxicity, and focal mineralization with associated hyperphosphatemia. Additional details can be found in the Investigator's Brochure.

7.2 Study Rationale

This first-in-human study is an open-label, multicenter, Phase 1, dose-finding study that will be conducted in 2 parts: a Dose Escalation phase (Part 1) and a Dose Expansion phase (Part 2). The primary objectives are to determine the MTD and/or the recommended Phase 2 dose (RP2D) of H3B-6527 and to assess the safety and tolerability of H3B-6527 as a single agent in subjects with advanced HCC.

H3B-6527 will be supplied as 50-, 100-, and 200-mg capsules and will be administered orally as a single-agent dose in 21-day cycles without a break; this is supported by nonclinical data showing tumor growth inhibition and regressions in human HCC xenograft models grown in nude mice. In addition, nonclinical safety evaluations with once daily (QD) dosing in mice and dogs have shown evidence of on-target pharmacology (eg, changes in circulating bile acid). The starting dose of 300 mg (first-in-human dose) is the human equivalent dose (HED) of 1/6th the highest non-severely toxic dose (HNSTD) in dog. The maximum single dose proposed in the current study is 2000 mg. It is also limited by the maximum number of capsules required to reach this dose.

The Dose Escalation Phase will follow a standard 3+3 cohort design. The dose will be escalated in successive cohorts based on a modified Fibonacci schema. The RP2D will be selected based on an integrated evaluation of available safety, tolerability, efficacy, pharmacokinetic (PK), and pharmacodynamic data for all dose levels on the defined schedule. The following considerations will help guide selection.

1. The RP2D must have <2/6 subjects experiencing a DLT at that dose (<33% DLT rate).

2. The overall safety profile, including AEs assessed as related to study drug treatment but not considered dose-limiting, as well as the nature, type, timing, and frequency of toxicities.

3. Tumor response(s).

4. Demonstration of proof of principle with respect to in vivo biologic activity. Mouse studies have shown an approximate 100-fold increase in cytochrome P450 (CYP) 7A1 tumor levels at efficacious doses. The proof of principle for H3B-6527 could be a robust increase in CYP7A1 tumor expression in humans.

Safety, tumor response, PK, and pharmacodynamic assessments will be performed on all subjects.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objectives of this study are to:

- Determine the MTD and/or RP2D of H3B-6527 in subjects with advanced HCC

- Assess the safety and tolerability of H3B-6527 as a single agent administered orally.

8.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the PK profile of H3B-6527
- Evaluate the preliminary antitumor activity of H3B-6527 at the RP2D and schedule in subjects with advanced HCC, who are FGF19-positive as determined by the Sponsor-designated laboratory.

8.3 Exploratory Objectives

The exploratory objectives of this study are to:

- Explore biomarkers and their correlation with safety and efficacy endpoints
- Assess the pharmacodynamic effects of H3B-6527 on FGF19, Ki67, bile acids, and other FGFR4-related biomarkers in blood
- Explore the relationship between PK and pharmacodynamics
- Exposure to H3B-6527 in tumor samples may be assessed
- Explore the metabolite profile of H3B-6527 in plasma and urine.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an open-label, multicenter, Phase 1 study that will be conducted in 2 parts: a Dose Escalation phase (Part 1) and a Dose Expansion phase (Part 2). Approximately 30 to 128 subjects are planned for enrollment. H3B-6527 will be administered by mouth (PO) in 21-day cycles without break to examine both QD and BID dose schedules, with flexibility to also examine additional alternate dosing schedules (eg, daily for 2 consecutive weeks every 3 weeks [dosing on Days 1-14 of a 21-day cycle]).

During both parts of the study, subjects will be administered the study drug with food based on the Healthy Volunteers Food-Effect study (Study H3B 6527-A001-001: A Randomized Phase 1 Food-Effect Study of H3B-6527 in Healthy Subjects). The starting dose of study drug when given with food was agreed upon with the Safety Review Committee (SRC) to meet the criteria that it be no more than one-half of the previously determined safe total daily dose level. Any additional dose escalation will follow the procedures outlined in Section 9.1.1.

The objective of Part 1, the Dose Escalation phase is to determine the MTD and/or RP2D of H3B-6527 in subjects with HCC. The total number of subjects to be enrolled will depend on the observed safety profile, which will determine the number of subjects per dose cohort, as

well as the number of dose escalations required to achieve the MTD and/or RP2D of H3B-6527.

This study makes provision for exploring a BID schedule of H3B-6527; the criteria to evaluate H3B-6527 at the BID dose schedule will be based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all QD dose levels tested. In this case, a new cohort of 3 subjects will be enrolled and treated with a BID dose. The initial total daily dose given BID will be equal to a total daily dose that has been well tolerated as a QD dose (DLT rate <33% in a cohort of 3-6 subjects).

During Part 2, the Dose Expansion phase, a sample size of 40 subjects per dose schedule will be enrolled to examine both QD and/or BID dosing of H3B-6527 based on the recommended dose determined from Part 1, the Dose Escalation Phase. When both dose schedules are accruing subjects, an alternating enrollment schema into QD and BID dose schedule will be followed.

Safety, tumor response, PK, and pharmacodynamic assessments will be performed on every subject; see Section 9.5 for details.

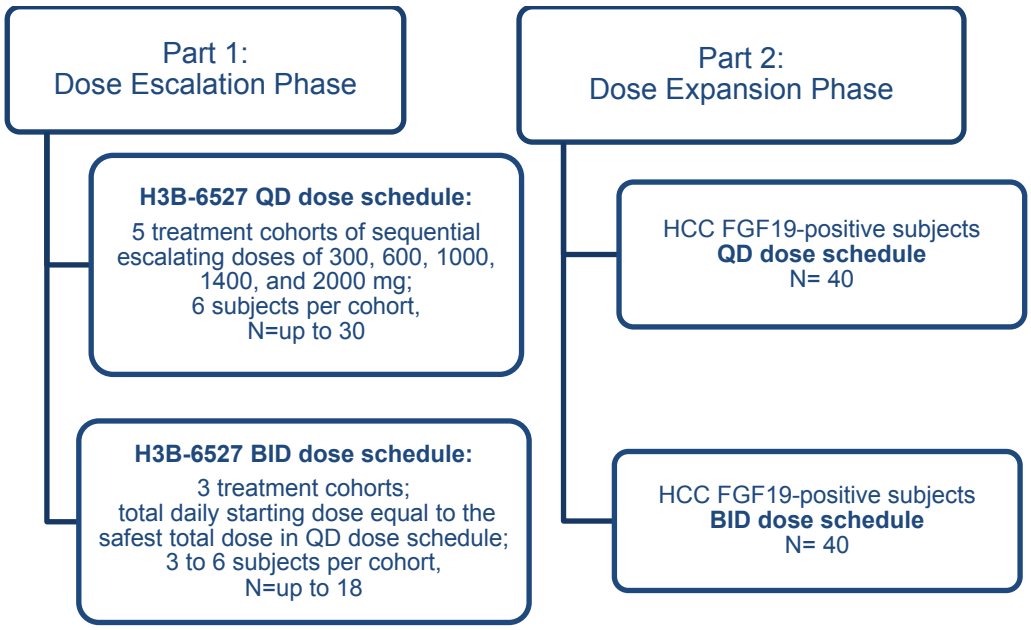


Figure 1: Overall Study Design

BID = twice daily, HCC = hepatocellular carcinoma, QD = once daily.

9.1.1 Study Parts

9.1.1.1 Dose Escalation (Part 1)

The objective of Part 1, the Dose Escalation phase, is to determine the MTD/RP2D of H3B-6527 in subjects with advanced HCC. The selection of the RP2D will be based on an integrated evaluation of safety, tolerability, and clinical benefit, including PK and pharmacodynamic data. The total number of subjects to be enrolled will depend on the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD and/or RP2D of H3B-6527. Assuming 5 dose levels will be studied for the QD dose schedule and 3 dose levels for the BID dose schedule and a maximum of 6 subjects will be enrolled per dose level, approximately 30 to 48 subjects may be accrued during dose escalation. Subjects enrolled into Part 1, Dose Escalation phase, are not required to be FGF19-positive.

The criteria to evaluate at the BID dose schedule will be based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all QD dose levels tested. In this case, a new cohort of 3 subjects will be enrolled and treated with a BID dose. The initial total daily dose given BID will be equal to a total daily dose that has been well tolerated as a QD dose (DLT rate <33% in a cohort of at least 3 subjects). If BID dosing of H3B-6527 is well tolerated in this initial cohort, then dose escalation may continue with BID dosing, following the same dose escalation rules applied to QD dosing. Additional cohorts of subjects may be enrolled to evaluate a less frequent dosing schedule (eg, daily for 2 consecutive weeks every 3 weeks [dosing on Days 1-14 of a 21-day cycle]).

Due to the potential for dropouts during the first cycle of treatment (eg, because of early disease progression), a cohort may initially be expanded to include up to 2 additional subjects. However, if these additional subjects are to be enrolled, they must start treatment ≤14 days after the third subject enrolled in the cohort was first dosed with H3B-6527. The decision to dose escalate may still be made after the third subject enrolled to the dose level in question has completed the first cycle of treatment. However, if under these circumstances the decision is made to enroll subjects to a higher dose level, and one of the additional subjects treated at the preceding dose level experiences a DLT in the first cycle of treatment, then further enrollment of subjects to the higher dose level will be suspended until it can be determined whether the preceding dose level exceeds the MTD. In the meantime, subjects enrolled to the higher dose level may continue treatment at that dose if they are tolerating it well, and if continuing treatment is considered appropriate for the toxicity in question.

For dose escalation purposes, toxicities assigned as DLTs during the first cycle will be assessed. After 3-6 subjects in a cohort have completed Cycle (C) 1, all available safety data will be reviewed by the SRC, consisting of Sponsor personnel and investigators, and the decision to proceed to the next dose cohort will be made jointly. If different dose schedules are explored, decisions regarding dose escalation will be made based on review of data from subjects enrolled in cohorts on the same schedule, however, safety data from alternate schedules may be considered by the SRC. Toxicities will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

Once a subject has completed C3 at the initially assigned dose schedule and dose level (QD or BID), intrapatient dose escalation will be allowed. Only subjects who have not progressed on treatment and did not have a dose reduction or interruption because of a drug-related AE, will be permitted to escalate to the highest dose level that has completed DLT assessment within that dose schedule and has been shown to be safe (no DLT in the first 3 subjects or no more than 1 DLT in 6 subjects). Subjects on the intrapatient dose escalation will not be included in the DLT analysis at the higher dose level. The investigator and the medical monitor must agree that dose escalation is appropriate for the subject prior to escalating their H3B-6527 dose level.

The starting dose of 300 mg QD (first-in-human dose) is the HED of 1/6th the HNSTD in dog. Dose escalation will follow a modified Fibonacci design such that the magnitude of the escalation will decrease as the dose level nears the HED of the HNSTD in dogs (HED ≈ 2000 mg).

Table 1 Dose Cohorts in H3B-6527 Dose-Escalation

Dose Level	Initial No. of Subjects	H3B-6527 Total Daily Dose
-1	3	150 mg
1[a]	3	300 mg
2	3	600 mg
3	3	1000 mg
4	3	1400 mg
5	3	2000 mg

These total daily dose levels may be evaluated in QD or BID dose schedules, including intermediate dose levels, and in expansion of an existing dose level of up to 12 evaluable subjects following discussions between the Sponsor and the investigators, if supported by evolving safety, tolerability, PK, and pharmacodynamic data.

BID = twice daily, PK = pharmacokinetic, QD = once daily.

a: Planned starting dose level in QD schedule.

Refer to Section 9.4.4.1 for details regarding the dose-escalation procedure.

The MTD is defined as the highest dose at which no more than 1 of 6 subjects experiences a DLT in the dose cohort. (Note that at least 6 subjects must be treated at the dose level potentially considered to be the MTD before that dose level can be considered the MTD). Therefore, if ≥2 subjects within a cohort experience a DLT and the previous dose level did not enroll 6 subjects, enrollment will move down to the previous dose level and continue until 6 subjects are enrolled, and the same guidelines for determining the MTD will be followed.

The RP2D may not exceed the MTD and will be agreed upon by the SRC, based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data, for all dose levels tested. Clinically significant toxicities (eg, chronic Grade 2 toxicities) or AEs that meet the definition of dose limiting but occurring after C1 (dose-modifying events,

DME) may be considered when determining the RP2D. Once the MTD/RP2D is reached, at least 6 HCC subjects must be enrolled at the RP2D (regardless of the total number of subjects enrolled at that dose level) to proceed with dose expansion.

To be evaluable for a DLT, subjects must have completed safety assessments through predose on C2 Day 1 and must have received at least 17 of 21 (approximately 80%) study days within C1, unless due to a DLT. Subjects who discontinue from the study for reasons other than DLT before completing C1 are to be replaced. Subjects who experience toxicities meeting DLT criteria during C1 will be discontinued from treatment. In rare cases, an exemption to study discontinuation for a DLT in 1st cycle may be considered after discussion between the treating physician, Sponsor and study medical monitor. Subjects who experience toxicities meeting DLT criteria may, at the discretion of the investigator and after discussion with the Sponsor, be allowed to continue study drug at a reduced dose if this is judged to be in the best clinical interest of the subject. The Sponsor will communicate information about DLTs or safety concerns rapidly to all sites as per the separate Dose Escalation Plan, which also details the format and timelines of the Dose Escalation review meetings, and the communication of dose level decisions to all sites.

9.1.1.1.1 DEFINITION OF DOSE-LIMITING TOXICITIES OR DOSE-MODIFYING EVENTS

DLTs are defined as any of the toxicities listed in Table 2 occurring during C1 Phase 1 only and judged by the investigator as related to study drug (ie, assessed as unrelated to disease, intercurrent illness, or concomitant medications). Any event that occurs in C2 or beyond (including any cycle in Phase 2) will be considered a DME.

Table 2 Definition of Dose-Limiting Toxicity (Cycle 1 Phase 1 Only) or Dose-Modifying Event (Cycle 2 or Beyond and Any Cycle in Phase 2)

TOXICITY	CRITERIA
Hematology	• Febrile neutropenia • CTCAE Grade 4 neutropenia that does not resolve to Grade ≤2 within 7 days • CTCAE Grade 3 thrombocytopenia requiring transfusion • CTCAE Grade 3 thrombocytopenia and clinically significant bleeding • CTCAE Grade 4 thrombocytopenia • CTCAE Grade 3 anemia if transfused or if lasting for more than 7 days • CTCAE Grade 4 anemia of any duration
Gastrointestinal	• CTCAE Grade 3 nausea, vomiting and/or diarrhea lasting more than 72 hours despite the use of optimal anti-emetic/antidiarrheal treatment • CTCAE Grade 4 diarrhea and/or vomiting irrespective of prophylaxis or appropriate treatment
Renal	• CTCAE Grade ≥3 serum creatinine
Hepatic	• CTCAE Grade 3 bilirubin (>3.0 ×ULN) and/or AST/ALT ≥10 ×ULN • For subjects with a starting AST/ALT within the normal range for the local laboratory, an elevation AST/ALT ≥ 5 ×ULN for the local laboratory

Table 2 Definition of Dose-Limiting Toxicity (Cycle 1 Phase 1 Only) or Dose-Modifying Event (Cycle 2 or Beyond and Any Cycle in Phase 2)

TOXICITY	CRITERIA
	• For subjects with an abnormal value ≥ ULN at baseline based on the local laboratory ranges, an AST/ALT elevation ≥ 10 ×ULN for the local laboratory
Other AEs not listed above	• Nonhematologic toxicities of CTCAE Grade ≥3 except for the following: – CTCAE Grade 3 fatigue lasting less than 1 week – Isolated CTCAE Grade 3 elevations in biochemistry laboratory values without associated clinical symptoms that last for ≤7 days. This includes electrolyte abnormalities that respond to medical intervention. • H3B-6527-related, CTCAE Grade 2 nonhematologic toxicities that, in the opinion of the treating investigator, require a dose reduction or discontinuation of study drug, or lead to a failure to complete at least 17 days of study drug administration in C1, may be deemed dose-limiting if agreed upon by the participating investigator and the Sponsor.

AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, C = Cycle, CTCAE = Common Terminology Criteria for Adverse Events, ULN = upper limit of normal.

As described in Table 2, any subject with an increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to ≥2 × the baseline value or with a bilirubin level of >3 ×the upper limit of normal (ULN) must have repeat testing 1 week later. If either the ALT or bilirubin level increase further, testing will be repeated at 1-week intervals until the values return to baseline levels.

The only instance in which the AST/ALT and/or bilirubin changes will not be considered a DLT is if there is unequivocal evidence that these increases are due to progression of the underlying disease or the intrahepatic malignancy. In these cases, determination of a non-DLT event will be made jointly by the Sponsor and the investigator(s).

For any dose-limiting hepatic toxicity that does not return to baseline within 7 days, an abdominal computed tomography (CT) scan must be performed to assess whether it is related to disease progression.

9.1.1.2 Expansion (Part 2)

Prior to starting Part 2 of the study, the investigators and the Sponsor will use safety, efficacy, PK, and pharmacodynamic data obtained during the Dose Escalation Phase, as well as clinical judgement, to jointly determine the dose schedules to be studied.

During Part 2, the Dose Expansion phase, approximately 40 subjects per dose schedule will be enrolled to examine QD and/or BID dose schedules. Subjects enrolled into Part 2, Dose Expansion phase, must be FGF19-positive as defined by Sponsor-designated laboratory.

Part 2 of the study is designed to better characterize the safety, tolerability and preliminary antitumor activity of the study drug when provided at the RP2D and schedule. For a reference of the precision of objective response rate (ORR) estimates, the associated 2-sided 95% CIs for ORR up to 30% for 40 subjects is provided. See Section 9.7.2 for additional

information. When both dose schedules are accruing subjects, an alternating enrollment schema into QD and BID dose schedule will be followed.

9.1.2 Study Phases

The study will be conducted in the following 4 phases: Pretreatment Phase, Treatment Phase, Extension Phase, and Follow-up Phase.

9.1.2.1 Pretreatment Phase

This pretreatment phase will last no longer than 28 days and includes:

- A **Screening Period** to establish protocol eligibility.
- A **Baseline Period** to establish disease characteristics before treatment.

9.1.2.2 Treatment Phase

The Treatment Phase will last for 1 treatment cycle of 21 days.

Subjects who are receiving study drug at the end of the Treatment Phase will continue to receive study drug in the Extension Phase (see Section 9.1.2.3).

9.1.2.3 Extension Phase

In the Extension Phase, subjects will continue to receive the same treatment and dose they received during the Treatment Phase, provided termination criteria are not met.

In both the Treatment and Extension Phases, subjects will discontinue study drug at the time of progressive disease (PD), development of unacceptable toxicity, withdrawal of consent, or termination of the study program by the Sponsor. However, subjects may continue to receive study treatment, as long as there is demonstrated clinical benefit, as judged by the investigator after discussion with the Sponsor, or until the end of the study. Disease progression will be determined by the investigator following relevant modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines. The mRECIST for this protocol harmonizes the original mRECIST criteria (Lencioni and Llovet 2010) using triphasic liver CT/magnetic resonance imaging (MRI; optimized for precontrast, arterial phase, and portal venous phase) and elements of Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer, et al., 2009).

9.1.2.4 Follow-Up Phase

After the Off-treatment Visit (OTV), all subjects who discontinue study treatment, regardless of their reasons for doing so, will be followed for survival via telephone (for those subjects who experience PD or initiate a new anticancer therapy) or office visit (for those subjects still undergoing tumor assessments). Subjects will be followed for survival approximately every 12 weeks for up to 12 months or until 6 cycles after last patient in, death, loss to follow-up, or withdrawal of consent, whichever occurs first. Subjects who discontinue study drug and

have not experienced PD will continue to undergo tumor assessments every 6 weeks until documented PD or another anticancer therapy is initiated.

The data cutoff for the primary analysis will occur once the last subject completes 6 cycles of investigational therapy. Subjects will be allowed to continue treatment until progression or the end of therapeutic benefit from the study drug as determined by Sponsor discussion with investigator.

The end of the study is defined as when the last ongoing subject completes their off treatment visit. The off treatment visit should occur 30 days after final dose with a window of ±3 days.

The maximum estimated period for each subject on treatment is anticipated to be approximately 4 months. However, subjects may continue to receive study treatment, as long as they demonstrate clinical benefit as judged by the investigator after discussion with the Sponsor or until the end of the study.

9.2 Discussion of Study Design, Including Choice of Control Groups

The goals of Phase 1 oncology studies include estimation of the initial safety and tolerability of a study drug, establishment of an MTD, and determination of a recommended range of doses for evaluation in future clinical studies, based on PK and pharmacodynamic effects (Ahn, 1998; ICH E8, 1997; Gatsonis and Greenhouse, 1992; Dillman and Koziol, 1992); the primary objectives of the current study are consistent with those typical of Phase 1 oncology studies.

During the Dose Escalation Phase of the study, a traditional 3+3 dose escalation design will be used. The dose escalation scheme to be followed is based on a modified Fibonacci sequence schema, which is commonly employed in Phase 1 dose-finding oncology studies (Storer, 1989). An integrated evaluation of safety, tolerability, PK, and pharmacodynamic data will be utilized to select the RP2D dose schedule to be employed during the Dose Expansion phase.

Preliminary assessment of activity or potential therapeutic benefit may be a secondary objective of Phase 1 studies (ICH E8, 1997). Consistent with this premise, a secondary objective is to evaluate the potential antitumor activity of H3B-6527. After identification of the MTD, the potential antitumor activity of H3B-6527 will be evaluated in Part 2, the Expansion phase, to determine whether there are any tolerability issues or antitumor activity associated with the use of H3B-6527 in subjects with HCC.

It is recommended that the effect of food intake on the rate and extent of absorption of an orally administered investigational drug be investigated as early as possible during drug development to optimize dose finding and to ensure optimal food recommendations for study drug administration. The decision was made to allow study drug administration in conjunction with a meal, and this was informed by the Healthy Volunteers Food-Effect study (H3B-6527-A001-001). The starting dose of study drug when given with food was agreed upon with the SRC to meet the criteria that it be no more than one-half of the previously

determined safe total daily dose level. Any additional dose escalation will follow the procedures outlined in Section 9.1.1.

Since the study drug is to be administered with food, all subjects will be required to fast 2 hours prior to pharmacodynamic assessments and have a meal prior to or in conjunction with study drug administration.

9.3 Selection of Study Population

Approximately 30 to 128 subjects are planned to be enrolled in this study: 30 to 48 during Part 1, the Dose Escalation phase, and up to 80 subjects in the Expansion phase (40 subjects per dose schedule). The total number of subjects to be enrolled in the Dose Escalation phase will be dependent upon the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD of H3B-6527 and establish the RP2D. The total number of subjects in the Dose Expansion Phase will be dependent on whether data collected during the Dose Escalation Phase of the study can clearly differentiate between one dosing schedule (QD or BID) or whether both schedules will continue being evaluated during the Dose Expansion phase.

Subjects who do not meet all the inclusion criteria or who meet any of the exclusion criteria will not be eligible for enrollment in the study.

9.3.1 Inclusion Criteria

In order to be eligible for participation in this study, subject must:

1. Be ≥18 years of age.
2. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
3. Have an HCC diagnosis with the following criteria:
   - Confirmed by available pathology records or current biopsy (confirmed diagnosis may be made by histological examination or by noninvasive criteria according to the European Association for the Study of the Liver or the American Association for the Study of Liver Disease Guidelines)
   - Advanced, unresectable, or recurrent
   - Progressing since the last antitumor therapy
   - Child-Pugh A classification
   - No clinically significant ascites
   - Must have received at least one prior standard-of-care therapy, unless contraindicated.
4. Must be FGF19-positive, as determined by a Sponsor-designated laboratory from a fresh tumor sample prior to enrollment in the Dose Expansion phase.
5. Have completed any prior chemotherapy, monoclonal antibody or immunotherapy (eg, tumor vaccine, cytokine, or growth factor given to control the cancer) at least 4 weeks or

5 half-lives (whichever is shorter) before study drug administration, and all AEs must have either returned to Baseline or resolved to Grade 0 or 1.

6. Have completed any prior definitive radiation therapy at least 3 weeks before study drug administration; any prior focal radiotherapy at least 2 weeks before study drug administration; and irradiated lesions should show evidence of size increase as defined in inclusion criterion #7 if they are intended to be followed as target lesions; any radiopharmaceutical therapy (strontium, samarium, and yttrium) must have been completed 8 weeks before study drug administration.
7. Have tumor tissue available as follows:
   a. Part 1, Dose Escalation: Tumor tissue (screening acquisition or archival tissue if available) is requested but not mandated.
   b. Part 2, Dose Expansion: Fresh tumor tissue must be available (collected up to 8 weeks before administration of H3B-6527 on C1 Day 1). Archival tissue if available is requested but not mandated.
8. Have measurable disease as follows:
   a. Part 1, Dose Escalation: Subjects may have measurable or nonmeasurable disease as defined by mRECIST.
   b. Part 2, Expansion: Subjects must have measurable disease meeting the following criteria:

      i. Subjects with HCC: At least 1 measurable target lesion according to mRECIST that meets the following criteria:

      - Hepatic lesion
        - The lesion can be accurately measured in at least one dimension as ≥1.0 cm
        - The lesion is suitable for repeat measurement
        - The lesion shows intratumoral arterial phase enhancement on contrast-enhanced CT or MRI
      - Nonhepatic lesion
        - Lymph node lesion that measures at least one dimension as ≥1.5 cm in the short axis, except for porta hepatis lymph node that measures ≥2.0 cm in the short axis
        - Non-nodal lesion that measures ≥1.0 cm in the longest diameter

      Lesions previously treated with radiotherapy or locoregional therapy must show radiographic evidence of disease progression by mRECIST to be deemed a target lesion.
9. Have left ventricular ejection fraction >50% on echocardiography or multiple-gate acquisition (MUGA) scan.
10. Have adequate renal function defined as serum creatinine <1.5 × ULN (or calculated creatinine clearance ≥50 mL/min per the Cockcroft and Gault formula).
11. Have adequate bone marrow function including:

a. Absolute neutrophil count (ANC) ≥1500/mm^3 (≥1.5 × 10^9/L)

b. Platelet counts ≥75,000/mm^3 (≥75 × 10^9/L)

c. Hemoglobin ≥9.0 g/dL (may have been transfused)

12. Have adequate liver function including:

a. Adequate blood coagulation as evidenced by an International Normalized Ratio ≤1.5.

b. Total bilirubin ≤1.5 × ULN.

c. ALT and AST ≤5 × ULN.

d. No evidence of biliary duct obstruction unless obstruction controlled by local treatment or, the biliary tree can be decompressed by endoscopic or percutaneous stenting with subsequent reduction in bilirubin to ≤1.5 × ULN.

13. Females must not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing).

14. Females of childbearing potential should avoid becoming pregnant and use highly effective contraception while on treatment and for at least 1 month after finishing treatment. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (eg, sexual abstinence, an intrauterine device, a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence (calendar, symptothermal, and post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation. Women using oral hormonal contraceptives should add a barrier method.

15. Be willing and able to comply with all aspects of the protocol.

16. Provide written informed consent prior to any study-specific Screening procedures.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Other malignancy active within the previous 2 years except for basal or squamous cell skin cancer, stage 1 prostate cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast that has completed curative therapy.
2. Current evidence of corneal disorder/keratopathy including but not limited to corneal epithelial thinning, bullous/band keratopathy, corneal abrasion, inflammation/ulceration, or keratoconjunctivitis (to be confirmed by ophthalmological examination). Pre-existing cataract is not a reason for exclusion.
3. Brain or subdural metastases are not eligible, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment.
4. Genetic diseases of the liver that may complicate review of safety data.
5. Known human immunodeficiency virus infection.
6. Uncontrolled significant active infections, except HBV or HCV. Subjects with HBV are eligible, but should be taking appropriate antiviral medication if indicated. Subjects with HCV are eligible but must not be taking any concomitant treatment for HCV while receiving H3B-6527.
7. Major surgery or other locoregional treatment within 4 weeks before the first dose of study drug or radionuclide treatment (eg, ^{90}Yttrium intra-arterial treatment) within 8 weeks before the first dose of drug administration.
8. Inability to take oral medication, or presence of malabsorption syndrome or any other uncontrolled gastrointestinal condition (eg, nausea, diarrhea, or vomiting) that might impair the bioavailability of H3B-6527. Subjects with prior gastric resection are eligible.
9. Use of any drug that is a strong inhibitor or inducer of the CYP3A4 enzyme or the P-glycoprotein transporter within at least 2 weeks before the start of study drug and during the conduct of the study unless there is an emergent or life-threatening medical condition that requires it.
10. Use of any drug known to prolong corrected QT (QTc) interval within at least 2 weeks before the start of the study drug and during the conduct of the study.
11. Treatment with proton pump inhibitors that cannot be discontinued 3 days prior to the start of study drug and during the course of the study; antacids are permitted except for calcium carbonate antacids (eg, Tums®).
12. Use of other investigational drugs within 28 days or at least 5 half-lives (whichever is shorter) before study drug administration.
13. Previous treatment with a selective FGF19-FGFR4 targeted therapy.

14. Use of any live vaccines against infectious diseases (eg, influenza, varicella) within 4 weeks (28 days) of initiation of study therapy.
15. Presence of gastric or esophageal varices requiring active treatment.
16. A clinically significant electrocardiogram (ECG) abnormality, including a marked baseline prolonged QTc interval (eg, a repeated demonstration of a QTc interval >450 ms).
17. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug; or cardiac arrhythmia requiring medical treatment (including oral anticoagulation).
18. Any other major illness, medical condition, or concomitant medication that, in the Investigator's judgment, will substantially increase the risk associated with the subject's participation in this study or would compromise the subject's ability to safely complete the study.
19. Males who have not had a successful vasectomy (confirmed azoospermia) or they and their female partners do not meet the criteria above (ie, not of childbearing potential or practicing highly effective contraception throughout the study period or for 90 days after study drug discontinuation). No sperm donation is allowed during the study period or for 90 days after study drug discontinuation
20. Hypersensitivity to the study drug or to any of the excipients.
21. Intolerance or hypersensitivity to both CT and MRI contrast material that would preclude the ability to acquire the triphasic liver imaging required by the protocol.
22. Inorganic phosphorus > ULN for the institution. Note: Subjects may be on treatment for hyperphosphatemia, but the levels must be normal at screening to participate in this study. Subjects with high levels on screening may subsequently be treated and rescreened and, should they have stable levels for 2 weeks prior to study, may enter the study.
23. Total or ionized serum calcium > ULN for the institution. Note: Subjects may be on treatment for hypercalcemia, but the levels must be normal at screening to participate in this study. Subjects with high levels on screening may subsequently be treated and rescreened and, should they have stable levels for 2 weeks prior to study, may enter the study.
24. Endocrine changes that may result in increases in calcium or phosphate, including, but not limited to, hyperparathyroidism and tumoral calcinosis.
25. Past medical history and/or current evidence of tumoral calcinosis or tissue calcification.
26. Use of calcium or vitamin D supplements or systemic corticosteroids. The duration between the last systemic corticosteroid administration and the first dose of study drug should be at least 2 weeks.
27. Hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption.

9.4 Treatments

9.4.1 Treatments Administered

All subjects will receive H3B-6527 at their assigned dose daily PO. For the purposes of this study, a cycle length is defined as 21 days.

9.4.2 Guidelines for Continuation of Treatment

Study drug should continue to be administered as planned unless a DLT has occurred. Subjects who experience a DLT during C1 will be discontinued from treatment. In rare cases, an exemption to study discontinuation for a DLT in 1st cycle may be considered after discussion between the treating physician, Sponsor and study medical monitor. If a subject should experience a DLT or DME (ie, an AE meeting the criteria for a DLT but occurring after C1) during the study then study treatment will be interrupted and subjects may, at the discretion of the investigator, and after discussion with the Sponsor, be allowed to continue study drug at a reduced dose, if the following criteria are met:

- ANC $\geq 1.0 \times 10^9$/L (1,000/mm^3)
- Platelet count $\geq 75 \times 10^9$/L (75,000/mm^3)
- All other nonhematologic treatment-related toxicities are Grade 0 or 1 (except alopecia) or return to baseline level
- Clinical benefit is being received, and
- Evidence of an otherwise favorable risk/benefit profile.

The magnitude of the dose reduction cannot be specified *a priori* since the actual doses evaluated and the dose-toxicity relationship will not be known until there is clinical experience with H3B-6527; however, a minimum reduction of 33% must be taken. The dose chosen will require discussion and agreement between the investigator and Sponsor following review of the relevant clinical data.

Dose reductions are allowed for all subjects. However, once the H3B-6527 dose has been reduced for a given subject, no re-escalation will be permitted for that subject.

A maximum of 2 dose reductions will be allowed as needed, but study treatment should not be resumed in the case of the following treatment-related events:

- Occurrence of a DLT in C1 except upon agreement with investigator, Sponsor and medical monitor. A dose reduction must be taken if treatment is resumed.
- CTCAE Grade 3 or 4 cardiac event
- Nonhematologic events of Grade 4 severity
- Dose delay of ≥21 days for a treatment-related event in C2 and beyond.

9.4.3 Identity of Investigational Product

H3B-6527 drug product for clinical studies is supplied as Swedish orange, opaque, hypromellose shell capsules, size 4 containing 50 mg, size 2 containing 100 mg, or size 0 containing 200 mg of H3B-6527 drug substance. The composition ratio of the capsule content is the same for the 3 strengths.

H3B-6527 capsules (28) are packaged in a 50-mL high-density polyethylene bottle with 2 g of desiccant and closed with a polypropylene screw cap.

9.4.3.1 Chemical Name, Structural Formula of H3B-6527

Test drug code: H3B-6527

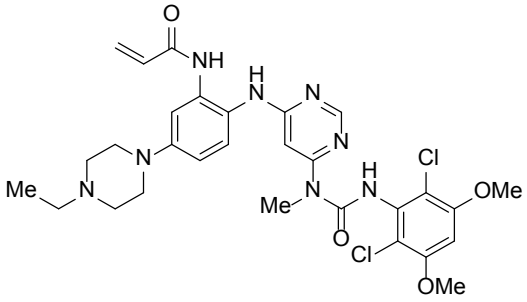
Generic name: Not assigned

Chemical name: N-(2-((6-(3-(2,6-dichloro-3,5-dimethoxyphenyl)-1-methylureido)pyrimidin-4-yl)amino)-5-(4-ethylpiperazin-1-yl)phenyl)acrylamide

Molecular formula: $C_{29}H_{34}Cl_2N_8O_4$

Molecular weight: 629.54

Structural formula: The structural formula is as follows:



Chemical Formula: $C_{29}H_{34}Cl_2N_8O_4$
Molecular Weight: 629.54

9.4.3.2 Comparator Drug

Not applicable.

9.4.3.3 Labeling for Study Drug

H3B-6527 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. Study drug labels will not bear any statement that is false or misleading in any

manner or represents that the study drug is safe or effective for the purposes for which it is being investigated.

9.4.3.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. At the study center, study drug is to be stored refrigerated at 2-8°C.

Subjects will be instructed to store study drug at home according to the storage requirements listed on the drug supply label.

While at the study center and at home, the study participants will be instructed to take capsules immediately after removal from refrigerated conditions, in order to limit the time out of the required storage conditions.

9.4.4 Method of Assigning Subjects to Treatment Groups

The dose level to which a subject is assigned is dependent on the study part and cohort into which the subject is enrolled.

9.4.4.1 Dose Escalation Scheme (Part 1)

The starting dose of H3B-6527 is 300 mg QD.

H3B-6527 doses will be escalated sequentially after the SRC, with appropriate representation from the Sponsor and participating investigators, reviews safety data collected during C1 from the subject(s) enrolled at the current dose level.

Subjects who do not receive study drug for at least 17 of 21 days (approximately 80%; not necessarily consecutively) during the first cycle for reasons not considered to be a DLT by both the investigators and the Sponsor will be replaced. The subjects who are replaced will not be considered evaluable for DLT assessments.

Based on the interim evaluation of the safety and tolerability data of the previous dose level, the Sponsor may decide to initiate accrual at an intermediate dose level. The SRC may be convened earlier at the discretion of the Sponsor if important safety issues arise requiring the attention of the committee.

Up to 3 subjects initially are to be enrolled. After 3 subjects complete C1 and have safety evaluations performed through C2 Day 1, and:

- None of these 3 subjects experience a DLT (see Section 9.1.1.1.1), then enrollment of the next cohort may commence with approval from the SRC.
- 1 of 3 subjects within a cohort experiences a DLT (see Section 9.1.1.1.1), then up to 3 additional subjects are to be enrolled sequentially at that dose level. If none of the

additional 3 subjects has a DLT (ie, 1 of 6 subjects has a DLT), then enrollment at the next scheduled dose may commence with approval from the SRC.

- If ≥2 subjects within a cohort experience a DLT (see Section 9.1.1.1.1), then the DLT dose level will have been reached and the previous lower dose level will be considered the MTD. Note that at least 6 subjects must be treated at the dose level potentially considered to be the MTD before that dose level can definitely be considered the MTD. Therefore, if ≥2 subjects within a cohort experience a DLT and the previous dose level did not enroll 6 subjects, enrollment will move down to the previous dose level and continue until 6 subjects are enrolled, and the same guidelines for determining the MTD will be followed.

  - Once the MTD or RP2D is established, additional subjects will be treated in the Expansion phase of the study (Part 2), which is designed to better characterize the safety, tolerability and preliminary antitumor activity of the study drug when provided at the RP2D and schedule.

Due to the potential for dropouts during the first cycle of treatment (eg, because of early disease progression), a cohort may initially be expanded to include up to 2 additional subjects. However, if these additional subjects are to be enrolled, they must start treatment ≤14 days after the third subject enrolled in the cohort was first dosed with H3B-6527. The decision to dose escalate may still be made after the third subject enrolled to the dose level in question has completed the first cycle of treatment. However, if under these circumstances the decision is made to enroll subjects to a higher dose level, and one of the additional subjects treated at the preceding dose level experiences a DLT in the first cycle of treatment, then further enrollment of subjects to the higher dose level will be suspended until it can be determined whether the preceding dose level exceeds the MTD. In the meantime, subjects enrolled to the higher dose level may continue treatment at that dose if they are tolerating it well, and if continuing treatment is considered appropriate for the toxicity in question. Although decisions regarding dose escalation will be made based on review of data from C1, safety data will also be collected from all subjects continuing treatment and this will be reviewed periodically by the SRC. Any detected cumulative toxicity may require later dose reductions or other action as appropriate, including further refinement of the RP2D.

The dose escalation procedure is summarized in Table 3.

Table 3 Summary of Dose Escalation Procedure

Observed Safety Outcomes	Action
Dose Escalation Cohorts (n=3-6 each)	
No DLT	• Escalate to the next planned dose level.
DLT in 1 of 3 subjects	• Expand cohort up to 6 subjects.
No additional DLT in 6 subjects	• Escalate to the next planned dose level.
DLT in ≥2 subjects	• MTD reached; stop dose escalation. • Possibly explore intermediate doses for the RP2D.

Note: DLT is defined in Section 9.1.1.1.1.
DLT = dose-limiting toxicity, MTD = maximum tolerated dose, RP2D = recommended Phase 2 dose.

If PK, pharmacodynamic, or safety data for H3B-6527 suggest that it may be preferable to administer H3B-6527 BID rather than QD, then the dose escalation procedure may be repeated for BID dosing. In this event, a new cohort of 3 subjects will be enrolled and treated with a BID dose; the initial total daily dose given BID will be equal to a total daily dose that has been well tolerated as a QD dose (DLT rate <33% in a cohort of 3-6 subjects). If BID administration of H3B-6527 is well tolerated in this initial cohort, then dose escalation may continue with BID dosing, following the same dose escalation rules applied to QD administration.

Furthermore, additional cohorts of subjects may be enrolled to evaluate a less frequent dosing schedule (eg, daily for 2 consecutive weeks every 3 weeks [dosing on Day -14 of a 21-day cycle]).

9.4.4.2 Expansion (Part 2)

In the Dose Expansion Phase, all subjects will receive H3B-6527 at the MTD or RP2D for a specific schedule as identified in the Dose Escalation Phase of the study.

9.4.5 Selection of Doses in the Study

The starting dose of H3B-6527, 300 mg (first-in-human dose), is the HED of 1/6th the HNSTD in dog. Dose escalation will follow a modified Fibonacci design such that the magnitude of the escalation will decrease as the dose level approaches the HED of the HNSTD in dogs (HED ≈2000 mg).

9.4.6 Selection and Timing of Dose for Each Subject

H3B-6527 will be supplied as 50-, 100-, and 200-mg capsules. The starting dose will be 300 mg/day PO, with escalation of total daily doses in successive cohorts to a maximum planned dose of 2000 mg (see Section 9.1.1.1).

During Parts 1 and 2, subjects will be instructed to take the dose in conjunction with a meal at approximately the same time each day (see Section 9.2).

Capsules should be swallowed whole. Dosing should not be repeated if a subject vomits. For subjects on a QD schedule, a dose missed by >8 hours should be skipped. For subjects on a BID schedule a dose missed by >4 hours should be skipped.

9.4.7 Blinding

The study will not be blinded.

9.4.8 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication Case Report Form (CRF) or Non-Pharmacological

Procedures CRF. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered.

9.4.8.1 Prohibited Concomitant Therapy and Procedures

The following therapies and procedures are prohibited during study participation:

- Other investigational drugs.
- Other antitumor therapies such as chemotherapy, surgical resection, or antitumor immunotherapy.
- Proton pump inhibitors.
- Radiotherapy for central metastases (eg, vertebral, mediastinal) will not be allowed; the need for such radiotherapy while on study will be seen as an indication of disease progression and the subject should be withdrawn from therapy. However, palliative radiotherapy for up to 2 local peripheral metastases not being used as target lesions is allowed but the need for such therapy may be an indication of PD and should be discussed with the Sponsor prior to implementation.
- Drugs that are strong inhibitors or inducers of CYP3A4 enzyme (see list in Table 4) or P-glycoprotein transporter.
- Drugs that raise serum calcium and phosphorus levels (eg, vitamin D supplements, calcium dietary supplements, calcium antacids) or systemic corticosteroids. The duration between the last systemic corticosteroid administration and the first dose of study drug should be at least 2 weeks. If a short-term course of systemic corticosteroids is required while on treatment, then study drug must be held while the subject receives systemic corticosteroid treatment. If the subject has not progressed in the interim, resumption of treatment with H3B-6527 may be considered following discontinuation of steroid treatment and a 2-week washout period.

Table 4 Inducers and Strong Inhibitors of CYP3A4

INDUCERS
Carbamazepine, efavirenz, nevirapine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, troglitazone
STRONG INHIBITORS
Indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone

Source: Indiana University Department of Medicine. http://medicine.iupui.edu/clinpharm/ddis/clinical-table Accessed September 7, 2016

9.4.8.2 Permitted Concomitant Therapy and Procedures

Medications and treatments other than those specified in Section 9.4.8.1, including palliative and supportive care for disease-related symptoms, are permitted during the study. Subjects should be closely monitored, and treatment is to be instituted for disease-related symptoms, as appropriate.

- Growth Factors: Subjects receiving recombinant erythropoietin or darbepoietin-α prior to study start may continue to receive pretreatment doses. Following initiation of study treatment, the use of erythropoietic and granulocyte growth factors is permitted in accordance with local practice or guidelines. American Society for Clinical Oncology guidelines may be implemented at the discretion of the treating physician.

- Management of diarrhea: Subjects should be instructed to take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. During the night, subjects may take 4 mg of loperamide every 4 hours. Subjects should be advised to avoid dehydration through adequate fluid intake. Bile acid sequestrants may be utilized in the case of bile acid diarrhea.

Medications for the treatment of AEs or cancer symptoms, eg, packed red blood cells and pain medications, are allowed. Additionally, medications (not addressed above) used to treat underlying medical conditions at study entry including antiemetics and antidiarrheals will be allowed to continue.

Management of hyperphosphatemia or hypercalcemia: Phosphorus and calcium will be measured at screening, before the first dose, every week with safety labs during C1, and on Day 1 and Day 8 for C2 and beyond. Please note that a treatment cycle is 21 days. Subjects with elevated levels of phosphorus or calcium at screening, as defined as being over the ULN on local lab ranges, may not participate in this study and should be referred for management of such. If successfully controlled, subjects may be rescreened. During study participation, any confirmed levels of phosphorus above 7 mg/dL, or calcium equal to or above Grade 2 hypercalcemia as per CTCAE, Version 4.03, will result in the dose of H3B-6527 being held for 14 days. The hyperphosphatemia and / or hypercalcemia should be managed by local practice, with medication, diet change and potential referral as necessary. After 14 days of holding the drug, if the phosphorus level has returned to 5.5 mg/dL or lower, and the calcium is less than or equal to a Grade 1 elevation, the subject may begin taking H3B-6527 again at one dose level lower than their original dose and should continue other measures initiated during the drug holiday, such as phosphorus lowering agents, while on study. If a subject should experience hyperphosphatemia above 7 mg/dL or hypercalcemia equal to or above Grade 2 again on study, then study therapy will be discontinued.

9.4.9 Treatment Compliance

A diary will be provided to subjects on C1 Day 1 to document the date and time of each study drug dose for all treatment cycles as well as the incidence of vomiting following administration. The investigator will review and document treatment compliance for each subject at each visit. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.10 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator or designee until the following documentation has been received by the Sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the Sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form 1572, where applicable
- Financial Disclosure form(s) for the PI and all subinvestigators listed on FDA Form 1572, where applicable
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license (in the US) or medical registration number on the CV
- A signed and dated clinical studies agreement

The investigator and the study staff will be responsible for the accountability of all study drug (dispensing, inventory, and record keeping) following the Sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drug to be used other than as directed by this protocol. Study drug will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drug, dispensing of study drug to the subject, collection and reconciliation of unused study drug that are either returned by the subjects or shipped to site but not dispensed to subjects,

and return of reconciled study drug to the Sponsor or (where applicable) destruction of reconciled study drug at the site. This includes, but may not be limited to, (a) documentation of receipt of study drug, (b) study drug dispensing/return reconciliation log, (c) study drug accountability log, (d) all shipping service receipts, (e) documentation of returns to the Sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the Sponsor. Any comparable forms that the site wishes to use must be approved by the Sponsor.

The study drug and inventory records must be made available, upon request, for inspection by a designated representative of the Sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare products Regulatory Agency). As applicable, all unused study drug and empty and partially empty containers from used study drug are to be returned to the investigator or designee by the subject and together with unused study drug that were shipped to the site but not dispensed to subjects are to be returned to the Sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the Sponsor for destruction of study drug and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drug to the central or local depot(s). Approval for destruction to occur at the site must be provided by the Sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the Sponsor's personnel, study drug that are to be returned to the Sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drug may be removed from the site and hand delivered to the central or local depot by Sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the Sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

Subjects will be evaluated for study eligibility during the Pretreatment period, within 28 days before the first H3B-6527 dose. All subjects must provide written informed consent before any study-related samples are collected or evaluations performed in this study, up to 8 weeks before the first dose of study drug.

9.5.1.1 Pretreatment Assessments

9.5.1.1.1 **SCREENING**

Subjects in the Dose Expansion phase will be evaluated for FGF19 expression. A fresh tumor biopsy (for determining FGF19 expression levels by a Sponsor designated laboratory), the signing of the ICF, and the collection of blood samples for pharmacodynamic analysis (same day as fresh tumor biopsy) will be required up to 8 weeks before administration of

H3B-6527 on C1 Day 1, in order to enroll in the Dose Expansion Phase of the study. The 28-day Screening Period will begin when any of the remaining screening assessments are performed. The entire Pretreatment Phase must be completed within 8 weeks of study drug administration on C1 Day 1. Subjects enrolled in the Dose Escalation phase are not required to be FGF19-positive.

9.5.1.1.2 DEMOGRAPHY

The subjects' demographic information will be collected during Screening. Demographic information includes date of birth (or age), sex, race/ethnicity.

9.5.1.1.3 MEDICAL HISTORY

Medical and surgical history and current medical conditions will be recorded at the Screening Visit and updated at Baseline, prior to administration of the first H3B-6527 dose. The medical history will also include cancer history (including the subject's primary tumor type, date of and stage at diagnosis, method of diagnosis, etiology) extent of disease (including portal vein invasion/thrombosis), and all previous treatments, including radiation therapy, and response to such treatment. As part of the subject's cancer history, study centers are to submit a local histology or cytology report obtained prior to enrollment, if available.

9.5.1.2 Efficacy Assessments

9.5.1.2.1 TUMOR IMAGING

All subjects are required to undergo chest, abdomen, and pelvis imaging at baseline and all follow-up time points. Contrast-enhanced CT scan of the chest and contrast-enhanced CT scan or MRI of the abdomen, pelvis, and any other areas of disease, as clinically indicated, will be acquired at Screening and at all imaging time points. A liver CT scan or MRI must be performed using triphasic scanning techniques optimized to capture precontrast, arterial, and portal venous phases. Copies of all tumor imaging scans must be retained by the investigators. If requested by the Sponsor or by the health authorities, these copies will be sent to an imaging core laboratory designated by the Sponsor for quality assessment, archiving, and potential future review. Historical standard-of-care scans conducted within 28 days prior to study drug administration may be used as screening/baseline imaging if scanning parameters are consistent with the requirements for this protocol as separately defined by the imaging core laboratory.

MRI scans (optimized for precontrast, arterial phase, and portal venous phase) may be used instead of CT scans for imaging of the abdomen and pelvis. However, the chest must be imaged using CT; and chest disease must be followed by CT scan (ie, chest x-ray for response assessment is not allowed). If iodinated intravenous (IV) contrast is contraindicated, chest CT scan should be performed without IV contrast.

Imaging studies are to be repeated during the Treatment Phase and Extension Phase every 6 weeks, or more frequently if clinically indicated, until disease progression, withdrawal of

consent, or the subject receives another anticancer therapy. The same method of assessment used during Screening must be used at all subsequent time points.

After initiation of treatment, if a subject is unable to undergo a contrast CT due to allergy or renal insufficiency, a chest CT scan without contrast, combined with MRI images of the remaining anatomy with gadolinium contrast, is preferred if tolerated by the subject. If it is determined that neither CT scan nor MRI IV contrast can be tolerated by the subject, a chest CT scan without contrast combined with high quality T1 and T2 weighted MRI images of the remaining anatomy, should be provided. Importantly, such a modality switch will render the subsequent measurements of target lesions, especially typical hepatic target lesions, inadequate and the target lesion disease should be followed as not evaluable or potentially progressing (if sufficient evidence is available).

CT and MRI scans should be of diagnostic quality acquired on spiral or multidetector CT with oral and IV contrast. Low-dose, noncontrast CT transmission scans from positron emission tomography/CT scanner are not acceptable. Spiral or multidetector CT scans should be performed with a 5-mm contiguous slice reconstruction algorithm. If MRI scans are acquired, contiguous 5-mm slice thickness with minimal gap are also recommended. Ultrasound should not be used for radiographic assessment. A chest x-ray or skeletal x-ray that clearly demonstrates a new metastatic lesion may be used to document progression in lieu of the CT/MRI scans.

A brain scan should be performed for all subjects to assess potential central nervous system disease and/or metastases as clinically indicated. For eligible subjects with previously treated brain metastases, a brain scan will be required at all tumor assessment time points (eg, every 6 weeks). For all subjects, a follow-up brain scan must be performed to confirm a complete response (CR) within 1 week following response confirmation.

If a subject discontinues treatment prior to C3 Day 1 (ie, 6 weeks after the first study drug dose on C1 Day 1), the scans for tumor assessment should be performed as close as possible to C3 Day 1, but before another anticancer therapy is initiated.

If a subject discontinues study treatment due to radiographic evidence of PD, then imaging studies are not required at the OTV.

During the Follow-up Period, subjects who discontinue study treatment without objective evidence of PD will continue to have tumor assessments (including brain scans as clinically indicated) performed every 6 weeks from the date of last tumor assessment, or sooner if clinically indicated, until PD is documented.

The tumor assessment schedule should not be affected by interruptions in therapy or any other events.

Tumor assessments will be performed following mRECIST guidance (Appendix 1) for HCC using triphasic liver CT/MRI (optimized for precontrast, arterial phase, and portal venous phase).

9.5.1.2.2 SURVIVAL

After the OTV, all subjects who discontinue study treatment, regardless of their reasons for doing so, will be followed for survival via telephone (for those subjects who experience PD or initiate a new anticancer therapy) or office visit (for those subjects still undergoing tumor assessments). Subjects will be followed for survival approximately every 12 weeks for up to 12 months or until 6 cycles after last patient in, death, loss to follow-up, or withdrawal of consent, whichever occurs first.

9.5.1.3 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Tumor tissue samples and blood samples for pharmacodynamics, pharmacogenomics (PG), and other biomarker assessments will be collected, as indicated in Table 6 and Table 7 except where prohibited by regional or local laws.

Instructions for the processing, storage, and shipment of PK, pharmacodynamic, PG, and other biomarker samples will be provided in the Laboratory Manual.

9.5.1.3.1 PHARMACOKINETIC ASSESSMENTS

Blood samples for PK assessments are to be collected from all subjects according to the schedule designated in Table 6 and Table 7. A protocol deviation will be reported only when a PK time point is not collected (missing) or blood is drawn on the wrong study day.

For subjects in Part 1, dose escalation, an aliquot of blood from the sample collected at each PK time point will be transferred for use for exploratory assessment of the metabolite profile of H3B-6527.

Plasma concentrations of H3B-6527 will be determined using a validated assay.

Additionally, urine samples for assessment of the metabolite profile of H3B-6527 will be collected during C1 from subjects in Part 1, dose escalation, only, according to the schedule designated in Table 6.

The total urine volume collected during each designated interval is to be documented in the CRF.

During the Dose Expansion phase, H3B-6527 levels in tumor tissue may be analyzed using a nonvalidated assay such as matrix-assisted laser desorption/ionization. During the Dose Escalation Phase, the investigators and Sponsor may agree that determination of H3B-6527 exposure in tumor tissue is required to guide dosing decisions. In this scenario, biopsies of tumor tissue will be obtained from all consenting subjects.

9.5.1.3.2 PHARMACODYNAMIC AND OTHER BIOMARKER ASSESSMENTS IN BLOOD

Blood samples for determination of biomarkers (in serum and/or plasma) will be collected from all subjects at the time points designated in Table 6 and Table 7.

Such samples may be analyzed for FGF19 (ligand of H3B-6527's target FGFR4), bile acids, circulating tumor cells, alpha-fetoprotein, and other exploratory biomarker candidates (both protein and nucleic acids) using global proteomic/metabolomics/genomic methods, enzyme-linked immunosorbent assay, multiplex bead-based immunoassay, or other assays/methods. These blood biomarker samples may be used for exploratory analysis for evaluation of response-related and/or safety-related outcomes, as well as for potential use in diagnostic development. Retrospective testing for potential subject stratification markers may also be explored.

During the dose escalation phase, results from biomarker studies may be used to aid the selection of the RP2D and schedule, and for monitoring drug efficacy. When new research results emerge, the parameters and methods for the pharmacodynamic biomarker analysis may change.

9.5.1.3.3 PHARMACODYNAMICS AND BIOMARKERS IN TISSUE

Archival Tumor Tissue Collection

For all subjects, an archival tumor tissue block or slide obtained before the first planned dose is to be collected, if available, any time during the study. Archival tumor tissue may be used for assessment of mutations and other exploratory biomarkers.

Screening Tumor Biopsy

Subjects in Part 1, the Dose Escalation phase, may have a fresh tumor sample, collected during Screening if an archival sample is not available; however, this is not a requirement for study participation.

For all subjects in the Expansion phase, the signing of the ICF, the collection of blood samples for pharmacodynamic analysis (same day as fresh tumor biopsy), and a fresh tumor tissue sample (for determining FGF19 expression levels by a Sponsor designated laboratory) ***is required*** to be collected up to 8 weeks before administration of the first dose of H3B-6527 on C1 Day 1. The 28-day Screening Period will begin when any of the remaining screening assessments are performed.

Additional Tumor Tissue Samples

In the event a subject is required to have a repeat tumor biopsy for medically indicated reasons, freshly obtained biopsy tissue from the procedure should be collected and shipped to H3 Biomedicine or a predesignated laboratory for exploratory biomarker analysis.

9.5.1.3.4 PHARMACOGENOMIC ASSESSMENTS

A blood sample will be collected at baseline for PG analysis. If the sample cannot be collected at baseline, it may be collected at any time point thereafter.

This sample may be used to evaluate the role of deoxyribonucleic acid (DNA) sequence variability on the absorption, distribution, metabolism, and elimination (ADME) of H3B-6527.

Furthermore, genomic DNA extracted from blood samples may be used to confirm whether the DNA sequence variants observed in DNA extracted from tumor material are limited to the tumor.

DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, ribonucleic acid, and protein) may be stored for up to 15 years to assist in any research scientific questions related to H3B-6527 or cancer.

9.5.1.4 Safety Assessments

Safety assessments include monitoring and recording all AEs, including SAEs; clinical laboratory tests (including hematology, coagulation parameters, clinical chemistry (including total bile acids, cholesterol, triglycerides), and urinalysis); and periodic measurement of vital signs, ECGs, MUGA/echocardiogram, and ophthalmic and physical examinations. Additionally, QTc intervals will be evaluated during the Dose Escalation phase.

AEs will be assessed using the National Cancer Institute CTCAE, Version 4.03.

9.5.1.4.1 **ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS**

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is H3B-6527.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)

- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the OTV (ie, within 30 days after the last study drug dose). Subjects who fail Screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition CRF. Serious AEs (SAEs) will be collected for 30 days after the last dose

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QT corrected for heart rate using Fridericia's formula (QTcF) interval is >450 ms and there is an increase of >60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 28 days or 5 ×the half-life, (whichever is longer) after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

AEs will be graded on a 5-point scale according to CTCAE, Version 4.03 (Appendix 2). Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments

- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.4.2 SERIOUS ADVERSE EVENTS AND OTHER EVENTS OF INTEREST

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for PK analysis should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.4.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, coagulation parameters, and urinalysis, are summarized in Table 5. The Schedules of Procedures/Assessments (Table 6 and Table 7) show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study. Clinical laboratory tests will be performed by the local laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

Screening laboratory assessments may be used as the Baseline assessment if performed within 72 hours before the first study drug dose. All hematology, blood chemistry (including pregnancy test, as applicable) and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle (refer to Section 9.4.2). Total bile acids will be collected with blood chemistries but, due to potentially long turnaround times, results are not required for individual subject treatment decisions prior to the start of each cycle. However, results should be reviewed when available. Additionally, total bile acids will be reviewed in aggregate to look for any potential safety trends as outlined in the existing safety review plan. The primary purpose of this retrospective review is to look for a potential correlation with clinical observations of related signs and symptoms.

Subjects should be in a seated or supine position during blood collection.

Table 5 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands/segs, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Coagulation Parameters	Prothrombin time or INR and activated partial thromboplastin time
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, total bilirubin
Renal function tests	Blood urea nitrogen, creatinine
Other	Albumin, calcium, carbon dioxide, cholesterol, glucose, lactate dehydrogenase, inorganic phosphorus, total protein, triglycerides, uric acid, total bile acids, AFP
Urinalysis	Appearance, specific gravity, and pH and semi-quantitative dipstick evaluation of glucose, protein, bilirubin, ketones, leukocytes, and blood. If dipstick evaluation is positive for leukocytes, protein, or blood, a microscopic examination of sediment is to be performed.

AFP = alpha-fetoprotein, INR = International Normalized Ratio, RBC = red blood cell, Segs = segmented cells, WBC = white blood cell.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.4.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], heart rate [HR; beats per minute], respiratory rate [RR; per minute], body temperature [in centigrade]), and weight (kg) will be obtained as designated in the Schedule of Procedures/Assessments (Table 6 and Table 7) by a validated method. BP, HR, and RR will be measured after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

Height (cm) is to be measured during Screening only.

When vital signs are to be obtained concurrently with PK or other blood samples, the vital sign measurements will be performed prior to drawing blood samples in order to maximize the accuracy of blood sampling times while minimizing the potential effects of blood drawing on recordings obtained during safety assessments.

9.5.1.4.5 PHYSICAL EXAMINATIONS

Comprehensive and symptom-directed physical examinations and ophthalmic examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 6 and Table 7). Documentation of the physical examination will be included in the source documentation at the site. Significant findings during the Pretreatment Period will be recorded on the Medical History and Current Medical Conditions CRF. Changes from pretreatment physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

Comprehensive Physical Examination

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. The subject will be queried regarding physical status and subjective symptoms as well. A urogenital examination will only be required in the presence of clinical symptoms related to this region.

Symptom-directed Physical Examination

The subject must be queried regarding changes in physical status since the last examination and a symptom-directed physical examination accordingly conducted.

Ophthalmic Examination

As part of the ophthalmological examination, a visual acuity test, funduscopic examination (mydriatic test if necessary), slit-lamp examination (fluorescein staining will be performed if necessary), and an anterior eye optical coherence tomography (OCT) for assessing the corneal epithelium will be performed. The central corneal thickness will be measured as part of the anterior eye OCT and recorded on the CRF. Any clinically significant changes in OCT will be captured and recorded as AEs. The ophthalmological examination may be completed within 7 days prior to Day 1 of each applicable cycle. Ophthalmic examinations performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen.

9.5.1.4.6 ELECTROCARDIOGRAMS AND HOLTER MONITORING

For all subjects, 12-lead ECGs will be obtained as designated in the Schedule of Procedures/Assessments (Table 6 and Table 7). In the event of any alteration, or if clinically necessary, an echocardiogram and/or cardiac enzymes should be performed.

In Part 1, Dose Escalation, the effects of H3B-6527 on cardiovascular repolarization will be evaluated via 12-lead continuous Holter/ECG monitoring on C1 Day 1 and on Day 8. The continuous Holter monitoring must begin at least 1 hour prior to dose on C1 Days 1 and 8 and will continue through 10 hours postdose for all subjects regardless of dose schedule (QD or BID) in the Dose Escalation Phase of the study.

Additionally, Holter monitoring/ECGs (12-lead) are to be collected 1 hour before the first dose (at 3 time points) and at 0.5, 1, 2, 4, 6, 8, and 10 hours postdose on C1 Days 1 and 8. At each of these time points, subjects should be supinely resting for at least 10 minutes before

and 5 minutes after the nominal time. When coinciding, blood collection, vital signs, and 12-lead safety ECGs should be performed immediately after the time window for ECG extraction.

Screening & baseline ECGs will be performed as singles. However, if clinically indicated, triplicates will be performed at screening and baseline. All other ECGs after screening/baseline will be performed as singles.

Individual ECGs will be extracted from the Holter recordings at specified time points per ECG manual and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for QTcF correction factors. The primary QTc parameter will be QTcF. Secondary parameters (QT corrected for heart rate using Bazett's formula [QTcB], QT, QRS, PR, and heart rate) and wave forms (T waves) will be evaluated.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.4.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

For ECG abnormalities meeting the criteria of an SAE (see Section 9.5.1.4.2), the site must fax or email the SAE report including the ECG report to the Sponsor using the SAE form (see Section 9.5.4.1).

9.5.1.4.7 ECOG PERFORMANCE STATUS

ECOG performance status is to be determined as designated in the Schedule of Procedures/Assessments (Table 6 and Table 7).

The ECOG performance status scale, with corresponding Karnofsky performance status score equivalents, is presented in Appendix 3.

9.5.1.4.8 ECHOCARDIOGRAM/MUGA

MUGA scans or echocardiograms will be performed during the Pretreatment Phase, at the OTV (±1 week), and if clinically indicated during treatment. MUGA scans or echocardiograms performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen. MUGA scans and echocardiograms will be performed locally in accordance with the institution's standard practice.

9.5.1.4.9 PREGNANCY TEST

A serum pregnancy test (β-hCG) will be performed during Screening for all premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A urine or serum pregnancy test will be performed before the first H3B-6527 dose and at the OTV.

9.5.2 Schedule of Procedures/Assessments

Table 6 presents the schedule of procedures/assessments for the Dose Escalation phase of the study. Table 7 presents the schedule of procedures assessments to be performed during the Dose Expansion Phase of the study.

Table 6 Schedule of Assessments in H3B-6527-G000-101 – Dose Escalation Cohort

Phase	Pretreatment[a]		Treatment			Extension			
Period	Screening	Baseline	Cycle 1			Cycle 2 and Beyond		Off-Treatment[b,c]	Follow-up
Visit	1	2	3	4	5	6, 8, etc.	7, 9, etc.	98	99
Day	-28 to -1	-3 to -1	1	8 (±3) [d]	15 (±3)	1 (±3)	8 (±3)		
Procedures/Assessments									
Informed consent	X[a]								
Demographics	X								
Inclusion/exclusion criteria	X	X							
Medical history	X	X							
Prior and concomitant medications	X	X	X	X	X	X	X	X	
Physical examination[e]	X	X	X	X	X	X	X	X	
Ophthalmologic examination[f]	X			X		X		X	
Echocardiogram / MUGA[g]	X		If clinically indicated					X	
Pregnancy test[h]	X		X					X	
Vital signs[i]	X	X	X	X	X	X	X	X	
ECOG performance status	X	X	X			X		X	
12-lead ECGs[j]	X	X	X			X		X	
ECG Holter monitoring[k]			X	X					
AFP biomarker assessment		X	Every 6 weeks through Cycle 6 with tumor assessment						
Hematology[l]	X	X	X	X	X	X	X	X	
Blood chemistry[l]	X	X	X	X	X	X	X	X	
Coagulation parameters[l]	X	X	X			X		X	
Urinalysis[m]	X		X			X		X	
PG blood sample[n]		X							
Metabolite profiling urine samples[o]				X					
PK and metabolite profiling blood samples[p]			X	X	X				

Phase	Pretreatment[a]		Treatment			Extension			
Period	Screening	Baseline	Cycle 1			Cycle 2 and Beyond		Off-Treatment[b,c]	Follow-up
Visit	1	2	3	4	5	6, 8, etc.	7, 9, etc.	98	99
Day	-28 to -1	-3 to -1	1	8 (±3) [d]	15 (±3)	1 (±3)	8 (±3)		
Procedures/Assessments									
Pharmacodynamic blood sample[q]		X	X	X	X	X	X	X	

Table 6 Schedule of Assessments in H3B-6527-G000-101 – Dose Escalation Cohort

Phase	Pretreatment[a]		Treatment			Extension			
Period	Screening	Baseline	Cycle 1			Cycle 2 and Beyond		Off-Treatment[b,c]	Follow-up
Visit	1	2	3	4	5	6, 8, etc.	7, 9, etc.	98	99
Day	-28 to -1	-3 to -1	1	8 (±3) [d]	15 (±3)	1 (±3)	8 (±3)		
Procedures/Assessments									
Pharmacodynamic blood sample for CTC/cf-nucleic acid[r]		X	X	X	X	X	X	X	
Archival tumor block or slides[s]		X							
Fresh tumor tissue biopsy[t]	X								
Brain scan[u]	If clinically indicated								
Tumor assessments: CT or MRI[v,w,x]	X		Every 6 weeks or sooner if clinically indicated					X	X
Adverse Events	Continuous from date of consent until off-treatment visit								
H3B-6527 administration[y]			Continuous 21-day cycles of H3B-6527 daily dosing.[y]						
Survival status[z]									X

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, β-hCG = beta-human chorionic gonadotropin, BID = twice daily, BP = blood pressure, BUN = blood urea nitrogen, C = Cycle, CF = cell-free, CR = complete response, CRF = case report form, CT = computed tomography, CTC = circulating tumor cell, ECG = electrocardiograms, ECOG = Eastern Cooperative Oncology Group, GGT = gamma-glutamyl transferase, HR = heart rate, ICF = informed consent form; IV = intravenous, LDH = lactate dehydrogenase, mRECIST = modified Response Evaluation Criteria In Solid Tumors, MRI = magnetic resonance imaging, MUGA = multigated acquisition, OCT = optical coherence tomography, OTV = off-treatment visit, PD = progressive disease; PG = pharmacogenomics, PK = pharmacokinetic, QD = once daily, RBC = red blood cell, RR = respiratory rate, WBC = white blood cell.

a: The Screening Period extends from Day -28 to Day -1, except for signing of the ICF, which may be up to 8 weeks before the first dose of study drug. The baseline assessments may be performed from Day -3 to Day -1 (before the first dose of H3B-6527). Screening assessments may be used as baseline assessments if performed within 72 hours of the first dose of study medication.

b: Subjects who discontinue study treatment for reasons other than PD will be followed until PD or death. All anticancer therapies will be collected. The Sponsor may choose to stop the collection of therapies after the first anticancer treatment.

c: The OTV should occur 30 days after the final dose of study drug with a window of ± 3 days.

d: Blood samples for PK analysis and urine samples **must be obtained on Day 8**. The window of **±3 days** does **not** apply to this visit for these samples.

e: A comprehensive physical examination will be performed during Screening and at the OTV. A symptom-directed physical examination will be performed on Day 1 of all treatment cycles and at any time during the study, as clinically indicated.

Table 6 Schedule of Assessments in H3B-6527-G000-101 – Dose Escalation Cohort

f: Ophthalmic examination by an ophthalmologist will be performed at Screening (or within 7 days prior to Day 1 of each applicable cycle), on C1 Day 8, C2 Day 1, and on Day 1 of all subsequent cycles (through C6), and at the off-treatment visit. Ophthalmic examinations performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen. After C6, OCT will be required only on Day 1 of every other cycle. As part of the ophthalmological examination, a visual acuity test, funduscopic examination (mydriatic test if necessary), slit-lamp examination (fluorescein staining will be performed if necessary), and an anterior eye OCT for assessing the central corneal thickness will be performed. The central corneal thickness will be measured as part of the anterior eye OCT and recorded on the CRF.

g: MUGA scans or echocardiograms will be performed during the Pretreatment Phase, during the OTV (window of ±1 week), and if clinically indicated during treatment. MUGA scans or echocardiograms performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen. MUGA scans and echocardiograms will be performed locally in accordance with the Institution's standard practice.

h: A serum pregnancy test (β-hCG) will be performed during Screening for all premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A urine or serum pregnancy test will be performed before the first H3B-6527 dose and at the OTV.

i: Vital signs include BP, HR, RR, and body temperature, as well as weight. BP, HR, and RR will be collected after the subject has been sitting for 5 minutes. Height will be measured during Screening only.

j: Screening and baseline ECGs will be performed as singles. However, if clinically indicated, triplicates will be performed at screening and baseline. All other ECGs after screening/baseline will be performed as singles.

k: Continuous Holter monitoring will begin at least 1 hour prior to dosing through 10 hours post-dose on C1 Days 1 and 8. Subjects should be supinely resting for at least 10 minutes prior to and 5 minutes after the following time points, pre-dose (3 time points within 1 hour of dose) and 0.5, 1, 2, 4, 6 ,8 and 10 hours postdose. When coinciding, blood draws, vital signs and 12-lead safety ECGs should be performed immediately after the time window for ECG extraction.

l: Hematology and blood chemistry samples will be obtained before drug administration. Screening assessments may be used as baseline assessments if performed within 72 hours of the first dose of study medication. Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential. Chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, GGT, LDH, ALT, AST, cholesterol, triglycerides, sodium, uric acid, and total bile acids. Total bile acids will be collected with blood chemistries but, results are not required for individual subject treatment decisions prior to the start of each cycle, but should be reviewed once available. Coagulation parameters (prothrombin time or International Normalized Ratio, and activated partial thromboplastin time) will be collected at within 72 hours of dosing on Day 1 of each cycle, and at the OTV.

m: Urine samples will be obtained before drug administration. Analysis will include assessment of appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood. Microscopic examination of sediment will be performed if urinalysis is positive for leukocytes, proteins, or blood.

n: Blood samples will be collected at baseline for PG analyses. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

o: Urine will be collected for exploratory metabolite profiling on Day 8, at the following collection intervals: 0 to 6 hours, 6 to 12 hours and 12 to 24 hours. Total urine volume collected during each interval will be recorded.

p: For QD dosing, blood samples for PK analysis will be collected in C1 on Day 1 and Day 8 at predose (0 hours), 0.5, 1, 2, 4, 6, 8, 10, and 24 hours (immediately prior to the next dose); and at Day 15 predose (0 hours). An aliquot of blood from each collection time point will be used for exploratory H3B-6527 metabolite profiling. For BID dosing, blood samples for PK analysis will be collected on C1 on Day 1 and Day 8 at predose (0 hours), 0.5, 1, 2, 4, 6, 8, and 10 hours (immediately prior to the next daily dose), and at Day 15 predose (0 hours). The ±3 day-window does not apply to the PK sampling on Day 8.

q: Blood samples for pharmacodynamic analysis (eg, circulating proteins, total bile acids) will be collected prior to dosing (all subjects will be required to fast 2 hours prior to pharmacodynamic assessments) at the following time points: Baseline, predose (0 hours) on C1 Day 1, Day 8, and Day 15, and Day 1 and Day 8 of subsequent cycles through cycle 6, and at the OTV.

Table 6 Schedule of Assessments in H3B-6527-G000-101 – Dose Escalation Cohort

r: Blood samples for nucleic-acid and CTC/cf based pharmacodynamic analysis will be collected prior to dosing (all subjects will be required to fast 2 hours prior to blood sample collection) at the following time points: Baseline, predose (0 hours) on C1 Day 1, Day 8, and Day 15, and Day 1 and Day 8 of subsequent cycles through cycle 6, and at the OTV.

s: An archival tumor tissue block or slide (if available) must be obtained any time during the study. Archival tumor tissue may be used for assessment of mutations and other exploratory biomarkers.

t: Subjects may have a fresh tumor sample collected during Screening if an archival sample is not available; however, this is not a requirement for study participation for the Dose Escalation Phase. In the event that a subject is required to have a repeat tumor biopsy for medically indicated reasons, freshly obtained biopsy tissue from the procedure should be collected and shipped to H3 Biomedicine or a predesignated laboratory for exploratory biomarker analysis as per instructions in the laboratory manual.

u: Screening CT/MRI of the brain should be performed as clinically indicated. For eligible subjects with previously treated brain metastases, a brain scan will be required at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed to confirm a CR within 1 week following response confirmation.

v: Tumor assessments will be performed based on mRECIST. CT scans (with oral and intravenous contrast) of chest, abdomen, pelvis and other known sites of disease will be obtained at Screening (within 28 days prior to C1/Day 1), every 6 weeks during the Treatment and Extension phases, and as clinically indicated. Subjects will also have triphasic liver CT or MRI performed (optimized for precontrast, arterial phase, and portal venous phase). Historical standard-of-care scans conducted within 28 days prior to dosing may be utilized as baseline imaging if scanning parameters are consistent with the requirements for this protocol.

w: MRI scans (optimized for precontrast, arterial phase, and portal venous phase) may be used instead of CT scans for imaging of the abdomen and pelvis. However, the chest must be imaged using CT; and chest disease must be followed by CT (ie, chest x-ray for response assessment is not allowed). If iodinated IV contrast is contraindicated, chest CT scan should be performed without IV contrast. The same method of assessment must be used at all time points as used at Screening.

x: The first radiological assessment of tumor response status will be performed at Week 6, unless there is clinical indication warranting earlier radiologic imaging. If subjects discontinue study treatment for radiographic evidence of disease progression, tumor assessments are not required at the off-treatment assessment. During the Follow-up Period, subjects who discontinue study treatment without objective evidence of disease progression, tumor assessments (including brain scans as clinically indicated) will continue to be performed every 6 weeks from the date of last tumor assessment, or sooner if clinically indicated, until documented disease progression or initiation of another anticancer therapy.

y: H3B-6527 should be taken daily at the assigned schedule and dose in conjunction with a meal. On visit days, subjects should not take study medication before evaluations are performed.

z: Subjects who discontinue study treatment will be followed for survival. Survival follow-up will be conducted approximately every 12 weeks for up to 12 months or until 6 cycles after last patient in, death, loss to follow-up, or withdrawal of consent, whichever occurs first.

Table 7 Schedule of Assessments in Study H3B-6527-G000-101 – Expansion Cohorts

Phase	Pretreatment[a]		Treatment			Extension			
Period	Screening	Baseline	Cycle 1			Cycle 2 and Beyond		Off Treatment[b,c]	Follow-up
Visit	1	2	3	4	5	6, 8, etc.	7, 9, etc.	98	99
Day	-28 to -1	-3 to -1	1	8 (±3)	15 (±3)	1 (±3)	8 (±3)		
Procedures/Assessments									
Informed consent	X[a]								
Demographics	X								
Inclusion/exclusion criteria	X	X							
Medical history	X	X							
Prior and concomitant medications	X	X	X	X	X	X	X	X	
Physical examination[d]	X	X	X	X	X	X	X	X	
Ophthalmologic examination[e]	X			X		X		X	
Echocardiogram / MUGA[f]	X		If clinically indicated					X	
Pregnancy test[g]	X		X					X	
Vital signs[h]	X	X	X	X	X	X	X	X	
ECOG performance status	X	X	X			X		X	
12-lead ECG[i]	X	X	X			X		X	
AFP biomarker assessment		X	Every 6 weeks through cycle 6 with tumor assessment						
Hematology[j]	X	X	X	X	X	X	X	X	
Blood chemistry[j]	X	X	X	X	X	X	X	X	
Coagulation parameters[j]	X	X	X			X		X	
Urinalysis[k]	X		X			X		X	
PG blood sample[l]		X							
PK blood samples[m]				X	X				
Pharmacodynamic blood sample[n]	X[a]	X	X	X	X	X	X	X	
Pharmacodynamic blood sample for CTC/cf-nucleic acid[o]	X	X	X	X	X	X	X	X	

Table 7 Schedule of Assessments in Study H3B-6527-G000-101 – Expansion Cohorts

Phase	Pretreatment[a]		Treatment			Extension			
Period	Screening	Baseline	Cycle 1			Cycle 2 and Beyond		Off Treatment[b,c]	Follow-up
Visit	1	2	3	4	5	6, 8, etc.	7, 9, etc.	98	99
Day	-28 to -1	-3 to -1	1	8 (±3)	15 (±3)	1 (±3)	8 (±3)		
Procedures/Assessments									
Archival tumor block or slides[p]		X							
Fresh tumor tissue biopsy[q]	X[a]								
Brain scan[r]	If clinically indicated								
Tumor assessments: CT or MRI[s,t,u]	X		Every 6 weeks or sooner if clinically indicated					X	X
Adverse Events	Continuous from date of consent until off-treatment visit								
H3B-6527 administration[v]			Continuous 21-day cycles of H3B-6527 daily dosing.						
Survival status[w]									X

AFP = alpha-fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, β-hCG = beta-human chorionic gonadotropin, BID = twice daily, BP = blood pressure, BUN = blood urea nitrogen, C = Cycle, CF = cell-free, CR = complete response, CRF = case report form, CT = computed tomography, CTCs = circulating tumor cells, ECG = electrocardiograms, ECOG = Eastern Cooperative Oncology Group, GGT = gamma-glutamyl transferase, HR = heart rate, ICF = informed consent form, IV = intravenous, LDH = lactate dehydrogenase, mRECIST = modified Response Evaluation Criteria In Solid Tumors, MRI = magnetic resonance imaging, MUGA = multigated acquisition, OCT = optical coherence tomography, OTV = off treatment visit, PD = progressive disease, PG = pharmacogenomics, PK = pharmacokinetic, QD = once daily, RBC = red blood cell, RR = respiratory rate, WBC = white blood cell.

a: The Screening Period extends from Day -28 to Day -1, except for signing of the ICF, the fresh tumor tissue biopsy, and the blood samples for pharmacodynamic analysis, which may be up to 8 weeks before the first dose of study drug. The 28-day Screening Period will begin when any of the remaining screening assessments are performed. The baseline assessments may be performed from Day -3 to Day -1 (before the first dose of H3B-6527). Screening assessments may be used as baseline assessments if performed within 72 hours of the first dose of study medication.

b: Subjects who discontinue study drug for reasons other than PD will be followed until PD or death. All anticancer therapies will be collected (the Sponsor may choose to stop the collection of therapies after the first anticancer treatment).

c: The OTV should occur 30 days after the final dose of study drug with a window of ± 3 days.

d: A comprehensive physical examination will be performed during Screening and at the OTV. A symptom-directed physical examination will be performed on Day 1 of all treatment cycles and at any time during the study, as clinically indicated.

Table 7 Schedule of Assessments in Study H3B-6527-G000-101 – Expansion

e: Ophthalmic examination will be performed by an ophthalmologist at Screening (within 7 days of Day 1 of each applicable cycle), on C1 Day 8, C2 Day 1, and on Day 1 of all subsequent cycles (through C6), and at the off-treatment visit. Ophthalmic examinations performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen. After C6, ophthalmic examination will be required on Day 1 of every other cycle. As part of the ophthalmological examination, a visual acuity test, funduscopic examination (mydriatic test if necessary), slit-lamp examination (fluorescein staining will be performed if necessary), and an anterior eye OCT for assessing the central corneal thickness will be performed. The central corneal thickness will be measured with the anterior eye OCT and recorded on the CRF.

f: MUGA scans or echocardiograms will be performed during the Pretreatment Phase, during the OTV (window of ±1 week), and if clinically indicated during treatment. MUGA scans or echocardiograms performed within 8 weeks of C1 Day 1 can be used in the event of a rescreen. MUGA scans and echocardiograms will be performed locally in accordance with the Institution's standard practice.

g: A serum pregnancy test (β-hCG) will be performed during Screening for all premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A urine or serum pregnancy test will be performed before the first H3B-6527 dose and at the OTV.

h: Vital signs include BP, HR, RR, and body temperature, as well as weight. BP, HR, and RR will be collected after the subject has been sitting for 5 minutes. Height will be measured during Screening only.

i: Screening and baseline ECGs will be performed as singles. However, if clinically indicated, triplicates will be performed at screening and baseline. All other ECGs after screening/baseline will be performed as singles.

j: Hematology and blood chemistry samples will be obtained before drug administration. Screening assessments may be used as baseline assessments if performed within 72 hours of the first dose of study medication. Hematology includes hemoglobin, hematocrit, RBC count, platelet count, WBC and differential. Chemistry includes albumin, alkaline phosphatase, total bilirubin, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, inorganic phosphorus, potassium, total protein, GGT, LDH, ALT, AST, cholesterol, triglycerides, sodium, uric acid, and total bile acids. Total bile acids will be collected with blood chemistries but, results are not required for individual subject treatment decisions prior to the start of each cycle, but should be reviewed once available. Coagulation parameters (prothrombin time or International Normalized Ratio, and activated partial thromboplastin time) will be collected at within 72 hours of Day 1 of each cycle, either at the Screening or Baseline visit, as well at the OTV.

k: Urine samples will be obtained before drug administration. Analysis will include assessment of appearance, specific gravity and pH as well as a semi-quantitative "dipstick" evaluation of glucose, protein, bilirubin, ketones, leukocytes and blood. Microscopic examination of sediment will be performed if urinalysis is positive for leukocytes, proteins, or blood.

l: A blood sample will be collected at Baseline for PG analyses. If it cannot be collected at the designated time point, it may be collected at a time point after baseline.

m: For QD dosing, blood samples for PK analysis will be collected in C1 on Day 8, at predose (0 hours), 0.5, 1, 2, 4, 6, 8, 10, and 24 hours (immediately prior to the next dose), and predose (0 hours) on Day 15. For BID dosing, blood samples for PK analysis will be collected on C1 on Day 8 at predose (0 hours), 0.5, 1, 2, 4, 6, 8, and 10 hours, and at Day 15 predose (0 hours). The ±3 day-window does not apply to the PK sampling on Day 8.

n: Blood samples for pharmacodynamic analysis (eg, circulating proteins, bile acids) will be collected prior to dosing (all subjects will be required to fast 2 hours prior to pharmacodynamic assessments) at the following time points: same day as fresh tumor biopsy, Baseline, predose (0 hours) on C1 Day 1, Day 8, and Day 15, and Day 1 and Day 8 of subsequent cycles. In addition, if a second biopsy is performed on a day other than C2 Day 1, the blood sample should also be collected on the same day as the biopsy. Samples will be collected through cycle 6 and at the end of treatment visit for all remaining patients.

o: Blood samples for nucleic acid- and CTC/cf-based pharmacodynamic analysis will be collected prior to dosing (all subjects will be required to fast 2 hours prior to blood sample collection) at the following time points: Screening, Baseline, predose (0 hours) on C1 Day 1, Day 8, and Day 15, and Day 1 and Day 8 of subsequent cycles. Samples will be collected through cycle 6 and at the end of treatment visit for all remaining patients.

Table 7 Schedule of Assessments in Study H3B-6527-G000-101 – Expansion

p: An archival tumor tissue block or slide obtained before the first planned dose in this study is to be collected, if available, any time during the study. Archival tumor tissue may be used for assessment of mutations and other exploratory biomarkers.

q: A fresh tumor tissue sample is required to be collected up to 8 weeks before administration of H3B-6527 on C1 Day 1, for determination of FGF19 expression levels by Sponsor-designated laboratory. Freshly obtained biopsy tissue from the procedure should be collected and shipped to H3 Biomedicine or a predesignated laboratory.

r: Screening CT/MRI scans of the brain should be performed as clinically indicated. For eligible subjects with previously treated brain metastases, a brain scan will be required at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed to confirm a CR within 1 week following response confirmation.

s: Tumor assessments will be performed based on mRECIST. CT scans (with oral and intravenous contrast) of chest, abdomen, pelvis and other known sites of disease will be obtained at Screening (within 28 days prior to C1/Day 1), every 6 weeks during the Treatment and Extension parts, and as clinically indicated. Subjects will also have triphasic liver CT or MRI performed (optimized for precontrast, arterial phase, and portal venous phase). Historical standard-of-care scans conducted within 28 days prior to dosing may be used as baseline imaging if scanning parameters are consistent with the requirements for this protocol.

t: MRI scans (optimized for precontrast, arterial phase, and portal venous phase) may be used instead of CT scans for imaging of the abdomen and pelvis. However, the chest must be imaged using CT scans; and chest disease must be followed by CT scans (ie, chest x-ray for response assessment is not allowed). If iodinated IV contrast is contraindicated, chest CT scan should be performed without IV contrast. The same method of assessment must be used at all time points as used at Screening.

u: The first radiological assessment of tumor response status will be performed at Week 6, unless there is clinical indication warranting earlier radiologic imaging. If subjects discontinue treatment for radiographic evidence of disease progression, tumor assessments are not required at the off-treatment assessment. During the Follow-up Period, subjects who discontinue study treatment without objective evidence of disease progression, tumor assessments (including brain scans as clinically indicated) will continue to be performed every 6 weeks from the date of last tumor assessment, or sooner if clinically indicated, until documented disease progression or initiation of another anticancer therapy.

v: On C1 Day 1, all subjects in the Expansion phase, will take H3B-6527 daily in conjunction with a meal. On visit days, subjects should not take study medication before evaluations are performed.

w: Subjects who discontinue treatment will be followed for survival. Survival follow-up will be conducted approximately every 12 weeks for up to 12 months or until 6 cycles after last patient in, death, loss to follow-up, or withdrawal of consent, whichever occurs first.

9.5.2.1 Description of Procedures/Assessments Schedule

The schedules of assessments are presented in Table 6 and Table 7, and details regarding the assessments to be performed are presented in Section 9.5.1.

9.5.3 Appropriateness of Measurements

Planned assessments are standard measurements for this type of study and are considered appropriate. Per the US FDA guidance, demographic data, complete subject medical histories, including cancer treatment history, and baseline disease status are to be for all subjects prior to administration of the first dose of study drug (FDA Guidance for Industry 2001; European Medicines Agency 2011). Study drug administration data, including dose interruptions and modifications and the associated reason(s), also are to be documented (FDA Guidance for Industry 2001; European Medicines Agency 2011).

AEs and SAEs will be monitored in this study in accordance with ICH GCP guidelines to ensure the safety of subjects. Furthermore, additional safety assessments conducted during this study, including physical examinations, ECGs, vital signs assessments, and clinical laboratory tests, are widely used and generally recognized as reliable, accurate, and relevant. These tests and procedures also will be monitored in accordance with ICH GCP guidelines.

Tumor response and progression will be assessed using standard criteria for the assessment of disease response in solid tumors.

The effects of H3B-6527 in FGF19 and other FGFR4-related biomarkers and any correlation with safety and antitumor activity will be evaluated during the study.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected through the OTV (ie, 30 days after the last study drug dose). All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the Sponsor regardless of the length of time that has passed since study completion.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the Sponsor or designee to be filed in the Sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion is considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

Study drug must be discontinued immediately for any subject who becomes pregnant during the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 REPORTING OF ADVERSE EVENTS ASSOCIATED WITH STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose.
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol.
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects.
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and reported using the procedures detailed in Section 9.5.4.1 even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF

9.5.4.4 Expedited Reporting

The Sponsor must inform investigators and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

AEs will be reported by the Sponsor or a third party acting on behalf of the Sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

The investigator may discontinue study drug for a subject at any time for safety or administrative reasons. A subject may elect to discontinue study drug and study participation at any time for any reason. All subjects who discontinue study drug are to complete the Off-Treatment visit, as indicated in the Schedule of Procedures/Assessments Table 6 and Table 7).

Study drug is to be discontinued for the following reasons:

- Progression of disease that, in the opinion of the investigator, precludes further study treatment. (After consultation with the Sponsor, H3B-6527 may be continued for a subject who has met the criteria for PD but, in the investigator's opinion, is receiving benefit.)
- Occurrence of an unacceptable AE.
- Subjects who do not receive study drug for at least 17 of 21 days (approximately 80%, not necessarily consecutively) during the first cycle for reasons not considered to be a DLT by both the investigators and the Sponsor will be replaced. The subjects who are replaced will not be considered evaluable for DLT assessments.
- Subject requires use of a prohibited concomitant medication or therapy.
- General or specific changes in the subject's condition unacceptable for further treatment within the study parameters, in the judgment of the investigator.
- Non-compliance.
- Lost to follow-up.
- Subject, investigator, or Sponsor request.

The reason for study drug discontinuation is to be documented in the CRF.

Subjects who discontinue study drug for reasons other than PD are to continue to have tumor measurements and disease response assessments performed every 6 weeks until the development of PD. After development of PD, subjects who discontinue study treatment, regardless of their reasons for doing so, will be followed for survival approximately every 12 weeks for up to 12 months or until 6 cycles after last patient in, death, loss to follow-up, or withdrawal of consent, whichever occurs first. However, subjects may continue to receive study treatment, as long as they demonstrate clinical benefit as judged by the investigator after discussion with the Sponsor or until the end of the study.

Study participation also may be discontinued for any of the following reasons:

- Subject withdrawal of consent
- Non-compliance
- Lost to follow-up
- Sponsor request
- Closure of the study by the Sponsor.

The reason for study discontinuation is to be documented in the CRF.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed by mail, telephone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, Standard Operating Procedures, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the Sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all

clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of H3 Biomedicine and should not be made available in any form to third parties without written permission from H3 Biomedicine, except for authorized representatives of H3 Biomedicine or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released. Statistical analyses will be performed using WinNonlin and SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan.

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the statistical analysis plan, which will be finalized before database lock.

9.7.1.1 Study Endpoints

The primary study endpoints are:

- Occurrence of DLTs as a function of the dose of H3B-6527 for determination of the MTD and RP2D.
- Safety/tolerability: the type and frequency of AEs, SAEs using CTCAE, Version 4.03, as well as changes in clinical laboratory values, ECG parameters, and vital sign measurements.

Secondary study endpoints are:

- PK: standard primary PK parameters including, but not limited to, the area under the plasma concentration-time curve from time 0 through the last measurable point (AUC_{0-t}), maximum observed plasma concentration (C_{max}) and time of maximum observed plasma concentration (t_{max}).
- Preliminary antitumor activity: Response will be determined by the investigator using mRECIST (Appendix 1). The following endpoints will be determined:

- ORR, defined as the proportion of subjects achieving a best overall confirmed response of partial response (PR) or CR (PR + CR), from first dose date until disease progression/recurrence.

- Duration of response, defined as the time from the date of first documented CR/PR until the first documentation of disease progression as determined by the investigator or death, whichever comes first.

- Progression-free survival (PFS), defined as the time from first dose date to the date of the first documentation of disease progression as determined by the investigator or death (whichever occurs first).

- Overall survival (OS), defined as the time from first dose date to the date of death.

- Time to response, defined as the time from first dose date to the date of first documented CR/PR.

Exploratory study endpoints include:

- Correlation of biomarker expression levels with antitumor activity and safety
- Expression levels of biomarkers in blood and tumor samples
- Correlation of biomarker expression levels with H3B-6527 exposure in plasma
- H3B-6527 levels in tumor tissue may be assessed
- H3B-6527 metabolites in plasma and urine

9.7.1.2 Definitions of Analysis Sets

Analyses will be performed using the following analysis sets:

- **Full Analysis Set**, which will include all subjects who receive at least 1 dose of study drug. This will be the primary analysis set for efficacy evaluations, as well as for demographic and baseline characteristics. The summary of efficacy will be based on this set for HCC subjects.

- **Safety Analysis Set**, which will include all subjects who received at least 1 dose of study drug. This will be the analysis set for all safety evaluations except DLT results.

- **PK Analysis Set**, which will include all subjects who have received at least 1 dose of study drug and have at least 1 evaluable plasma concentrations.

- **Pharmacodynamics Analysis Set**, which will include all subjects who have received at least 1 dose of study drug and have evaluable pharmacodynamic data.

- **PK/Pharmacodynamics Analysis Set**, which will consist of all subjects in the Safety Analysis Set that also have evaluable plasma PK and pharmacodynamic pretreatment assessment and at least 1 posttreatment assessment.

- **Response Evaluable Set**, which will consist of those HCC subjects who have received at least 1 dose of study drug and have measurable disease at baseline and at least 1 postbaseline evaluation.

9.7.1.3 Subject Disposition

The numbers of subjects screened for participation and number enrolled overall and by study part will be tabulated along with the proportion included in each analysis population. The proportion of subjects who discontinue the study will be tabulated, along with the primary reason for discontinuation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and baseline disease characteristic data will be summarized descriptively. Data to be tabulated will include at least demographic features such as sex, age, and race as well as weight and disease-specific status and medical history.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the current version of the WHO Drug Dictionary. The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Full Analysis Set by study part and cohort and overall, Anatomical Therapeutic Chemical class (ie, anatomical class, therapeutic class, pharmacologic class, chemical class), and WHO Drug Dictionary preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that started after the date of the first dose of study drug up to 30 days after the subject's last dose. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

The efficacy analyses will be performed at the time of data cutoff for primary analysis.

ORR, response duration, time to response, PFS, and OS will be listed and descriptively summarized as appropriate. All efficacy parameters will be summarized for the Full Analysis Set for HCC subjects. In addition, ORR, duration of response, and time to response will also be summarized for the Response Evaluable Set as appropriate.

ORR will be reported in summary tables.

For response duration and time to response, summary statistics (median Q1, Q3 and range) will be generated on subjects achieving a best overall response of PR or CR (PR + CR). The summary statistics will be generated using Kaplan-Meier estimate.

For PFS, subjects who do not have progression of disease or death information will be treated as right-censored observations at the time of the last response evaluation. The PFS censoring rules will follow the FDA guidance. PFS will be reported in both summary tables and plotted with Kaplan-Meier curve.

For OS, time of death will be censored for subjects who are without death information at the time of OS analysis. OS will be reported in both summary tables and plotted with Kaplan-Meier curve.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Plasma concentrations of H3B-6527 will be tabulated and summarized by dose level, day, and time. H3B-6527 PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: C_{max}, t_{max}, AUC_{0-t}, accumulation ratio (R_{acc}); and if data permit, area under the plasma concentration-time curve extrapolated to infinity (AUC_{0-inf}), terminal elimination half-life ($t_{½}$), apparent total body clearance (CL/F), and apparent volume of distribution during the terminal phase (V_z/F).

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Pharmacodynamics, PG and other biomarker analyses may be performed and reported separately. Details of these analyses will be described in a separate analysis plan.

9.7.1.8 Safety Analyses

Evaluation of safety will be performed on the Safety Analysis Set except for the determination of the MTD during the dose escalation. The determination of the MTD will be based on all DLT-evaluable subjects enrolled in the Dose Escalation part.

Subjects who do not receive study drug for at least 17 of 21 days (approximately 80%; not necessarily consecutively) during the first cycle for reasons not considered to be a DLT by both the investigators and the Sponsor will be replaced. The subjects who are replaced will not be considered evaluable for DLT assessments.

Safety data to be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and the results of ophthalmic examinations.

Safety parameters will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, and range for continuous variables; numbers and percentages for categorical measures).

The effects of H3B-6527 on cardiovascular repolarization will be evaluated via 12-lead continuous Holter/ECG monitoring on C1 Day 1 and on Day 8 in the Dose Escalation phase

of the study only. Individual ECGs will be extracted from the Holter recordings at specified time points per ECG manual and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for QTcF correction factors. The primary QTc parameter will be QTcF; secondary parameters (QTcB, QT, QRS, OTcB, PR, and heart rate) and waveforms (T waves) will be evaluated.

9.7.1.8.1 EXTENT OF EXPOSURE

Descriptive statistics for subjects treated, including the duration of treatment, the number of cycles received, and the number of subjects requiring dose changes, will be presented. A by-subject listing of the date of study drug administration and the dose administered will be presented.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 18.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized overall and by study part and cohort. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum CTCAE grade.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT overall and for each study part and cohort. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT overall and for each study part and cohort. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT overall and for each study part and cohort. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

In DLT-evaluable subjects, the number (percentage) of subjects with DLT will be presented by dose level for Dose Escalation phase of the study. Listing of subjects with DLT will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.4.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and study part and dose cohort using descriptive statistics. Qualitative parameters listed in Section 9.5.1.4.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Furthermore, the frequency of laboratory abnormalities by maximum postbaseline CTCAE grade will be tabulated by cycle and overall for selected laboratory parameters to include at least hemoglobin, white blood cell count, ANC, lymphocytes, platelet count, AST, ALT, bilirubin, creatinine, alkaline phosphatase, and electrolytes. Shift tables will also be produced for these parameters based on the baseline CTCAE grade and the maximum CTCAE grade overall and by cycle.

9.7.1.8.4 VITAL SIGNS

Changes in vital sign parameters (including systolic and diastolic BP, HR, RR, and temperature) and body weight will be summarized over time, and any abnormal values will be tabulated.

9.7.1.8.5 ELECTROCARDIOGRAMS AND HOLTER MONITORING

For all subjects, shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to end of treatment.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 ms
- QTc interval >480 ms
- QTc interval >500 ms

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 ms
- QTc interval increases from baseline >60 ms

All ECG abnormalities will be listed on a per-subject basis.

9.7.2 Determination of Sample Size

Dose Escalation Phase (Part 1)

It is anticipated that selection of the RP2D will be based on an integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data. The total number of subjects to be enrolled is dependent upon the observed safety profile, which will determine the number of subjects per dose cohort, as well as the number of dose escalations required to achieve the MTD and/or RP2D. For each dose schedule of QD and BID, assuming 5 dose levels for QD dose schedule and 3 dose levels for the BID dose schedule will be studied and a maximum of 6 subjects will be enrolled per dose level, then between 30 to 48 subjects may be accrued during dose escalation.

Dose Expansion Phase (Part 2)

A total of approximately 40 to 80 subjects will be enrolled in the Dose Expansion phase. Prior to starting the Dose Expansion phase, the investigators and the Sponsor will use safety, efficacy, PK, and pharmacodynamic data obtained during the Dose Escalation Phase, as well as clinical judgement, to jointly determine the dose schedules to be studied.

During Part 2, the Dose Expansion phase, a sample size of 40 evaluable subjects per dose schedule will be enrolled to examine QD and/or BID dosing of H3B-6527 based on the recommended dose determined from Part 1 (Table 8). For a reference of the precision of ORR estimates, the associated 2-sided 95% CIs for ORR up to 30% (40 subjects) are provided in Table 9.

This study makes provision for exploring a BID schedule of H3B-6527 during the Dose Expansion phase if evaluation of the PK, pharmacodynamics, or safety of H3B-6527 suggests that it may be preferable to administer H3B-6527 BID rather than QD. When both dose schedules are accruing subjects, an alternating enrollment schema into QD and BID schedule will be followed.

Table 8 Treatment Arms for Part 2, Dose Expansion

Treatment Arm	Number of Subjects
1: Subjects with advanced HCC who are FGF19-positive to receive H3B-6527 QD for 21-day cycles	40 subjects
2: Subjects with advanced HCC who are FGF19-positive to receive H3B-6527 BID for 21-day cycles	40 subjects

BID = twice daily, HCC = hepatocellular carcinoma.

Table 9 2-sided 95% Confidence Interval for ORR estimate up to 30% (40 subjects)

ORR (N=40)	2-sided 95% CI
5% (2 responders in 40 subjects)	(0.006, 0.169)
7.5% (3 responders in 40 subjects)	(0.016, 0.204)
10% (4 responders in 40 subjects)	(0.028, 0.234)
12.5% (5 responders in 40 subjects)	(0.042, 0.268)
15% (6 responders in 40 subjects)	(0.057, 0.298)
17.5% (7 responders in 40 subjects)	(0.073, 0.328)
20% (8 responders in 40 subjects)	(0.091, 0.356)
22.5% (9 responders in 40 subjects)	(0.108, 0.385)
25% (10 responders in 40 subjects)	(0.127, 0.412)
27.5% (11 responders in 40 subjects)	(0.146, 0.439)
30% (12 responders in 40 subjects)	(0.166, 0.465)

CI = confidence interval, ORR = objective response rate.

Within each treatment arm, if both QD and BID dose schedules are studied, an evaluation using efficacy, safety, PK, pharmacodynamic data will be performed and the investigators and Sponsor will jointly determine if one dose schedule is better than the other.

9.7.3 Interim Analysis

There will be interim analyses to define the MTDs and/or RP2Ds prior to initiating the Expansion phase of the study. Other interim analyses may be performed to determine if a different dosing schedule (eg, BID) or frequency (eg, 2-weeks on/1-week off) may be preferable. Database locks are not required to perform these analyses. Safety and PK summaries may be provided periodically.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

There are to be no changes to the protocol without written approval from the Sponsor. Protocols will be followed as written.

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the Sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the Sponsor's medical monitor (or appropriate study team member) and the IRB/IEC for the site must be notified immediately. The Sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC should be kept informed of such changes as required by local regulations. In these cases, the Sponsor may be required to send a letter to the IRB/IEC and the CA detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The CRA representing the Sponsor will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the Sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as x-rays and other imaging reports (eg, sonograms, CT scans, MRIs, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests), regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the Sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the Sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the Sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the Sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the Sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the PI (or a designated pharmacist) by the Sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the Sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the Sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the CRA representing the Sponsor or, when approval is given by the Sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the Sponsor/CRO and the Institution/investigator. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the Sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the Sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the Sponsor. These obligations of confidentiality and nonuse shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the Sponsor/CRO and the Institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and nonuse set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the Institution/investigator and the Sponsor/CRO.

11.11 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the Sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the Sponsor, the investigator should inform the Institution where applicable, and the investigator/institution should promptly inform the Sponsor and the IRB/IEC and provide the Sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The Sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Modified Response Evaluation Criteria in Solid Tumors

Tumor assessments will be performed following Modified Response Evaluation Criteria in Solid Tumors guidance (Lencioni and Llovet, 2010) using triphasic liver computed tomography (CT)/magnetic resonance imaging (MRI; optimized for precontrast, arterial phase, and portal venous phase) and elements of Response Evaluation Criteria in Solid Tumors, Version 1.1 (Eisenhauer, et al., 2009).

Quantitative and Qualitative Assessments of Tumor Burden

The disease burden during Screening will be categorized into target and nontarget lesions. Within the target and nontarget categories are typical hepatic lesions, atypical hepatic lesions, and nonhepatic lesions.

- Typical hepatic lesions are lesions that display hypervascularity in the arterial phase and "wash-out" in the portal venous phase of contrast-enhanced CT or MRI imaging.
- Atypical hepatic lesions are lesions that are not showing the distinctive enhancement pattern but are considered to be malignant.
- Nonhepatic lesions are all nodal and non-nodal lesions outside of the liver.

Selection and Measurement of Target Lesions

A maximum of 2 target lesions per organ and 5 target lesions in total, representative of all involved organs, may be selected. Target lesions are lesions that can be accurately measured in at least 1 dimension and whose minimum lesion size is as follows:

- Typical hepatic target lesions: The longest diameter of the viable tumor must measure ≥1 cm or ≥2 times the slice thickness/reconstruction interval (if the slice thickness/reconstruction interval is >5 mm).
- Atypical hepatic target lesions: The longest diameter must measure ≥1 cm or ≥2 times the slice thickness/reconstruction interval (if the slice thickness/reconstruction interval is >5 mm).
- Nonhepatic non-nodal target lesions: The longest diameter must measure ≥1 cm or ≥2 times the slice thickness/reconstruction interval (if the slice thickness/reconstruction interval is >5 mm).
- Nonhepatic nodal target lesions (lymph nodes): The short axis must measure ≥1.5 cm with exception of porta hepatis lymph nodes that need to be ≥2.0 cm in the short axis (regardless of modality/scanner type and slice thickness/reconstruction interval).

If typical and atypical liver lesions are present, preference should be given to typical liver lesions when selecting targets. Target lesions are measured at every time point and a single Sum of Diameters (SOD) will be determined by adding the longest diameters of all

non-nodal lesions and short axes (ie, widest dimensions perpendicular to the long axis) of nodal nonhepatic lesions. For typical hepatic lesions the longest diameters will include only the viable tissue, while for all other target lesions all tumor tissue (whether necrotic or not) will be included in the SOD. Note that hypovascular tissue should not be considered as necrotic (nonviable) tissue. While hypovascular tissue will still show contrast uptake (although less than what would be observed in a hypervascular lesion), necrotic tissue will show complete absence of any contrast enhancement. Quantitative determinations of average Hounsfield Units (HU) in the tissue of interest both precontrast and postcontrast may be used, if needed, to support the subjective assessment: necrotic (nonviable) tissue will show no change in HU between the phases, while hypovascular tissue will yield an increase in HU (although less than what would be observed in a hypervascular lesion) between precontrast and postcontrast images of the same region.

Target lesions are assessed as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), or not evaluable (NE) at every time point based on the SOD.

Selection and Assessment of Nontarget Lesions

Nontarget lesions are all other lesions, including malignant portal vein thrombosis, infiltrative type, and diffuse type hepatocellular carcinoma (HCC) with ill-defined lesion borders and truly nonmeasurable lesions. Nontarget lesions will be assessed qualitatively, and the possible assessments are CR, Non-CR/Non-PD (NN), and PD.

If a hepatic nontarget lesion exhibits an enhancement pattern that is consistent with HCC, the determination of CR, NN, PD, or NE will be dependent on the enhancing portion of the lesion.

If pleural effusions or ascites selected as nontarget lesions at Baseline are stable in size or minimally enlarging, they will be assessed as NN. A cytopathological confirmation of any effusion that appears or worsens on treatment is required when the measurable tumor has met criteria for response or SD.

New Lesions

New lesions are defined as:

- Unequivocally new nonhepatic lesions seen at follow-up, without a corresponding lesion on the baseline imaging
- New typical hepatic lesions displaying intratumoral arterial enhancement (hypervascularization in the arterial phase and washout in the portal venous phase on contrast-enhanced CT or MRI) that measure ≥1 cm in the longest diameter
- New atypical hepatic lesions ≥1 cm in the longest diameter that show interval growth in subsequent scans of at least 1 cm

Any lesion that meets the requirements for unequivocal new lesions will trigger PD. Any lesion that does not meet the above criteria (eg, <1 cm in longest diameter and/or does not show typical HCC vascular enhancement pattern) should be considered an equivocal new lesion. If an equivocal lesion is later determined to be unequivocal, the time point of progression will be the time point the lesion was first noted as equivocal.

Table 10 Overall Response Assessments per mRECIST

Target Lesions	Nontarget Lesions	New Lesions	Overall Time Point Response
CR	CR	No	CR
CR	NN	No	PR
CR	NE	No	PR
PR	NE	No	PR
PR	CR	No	PR
PR	NN	No	PR
SD	NE	No	SD
SD	CR	No	SD
SD	NN	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
NE	Non-PD	No	NE
CR	No nontarget lesions identified	No	CR
PR	No nontarget lesions identified	No	PR
SD	No nontarget lesions identified	No	SD

CR = complete response, mRECIST = modified Response Evaluation Criteria In Solid Tumors, NE = not evaluable, NN = non-CR/non-PD, PD = progressive disease, PR = partial response, SD = stable disease.

Appendix 2 Common Terminology Criteria for Adverse Events (v4.03)

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 [published 28 May 2009 (Version 4.03: 14 June 2010)] provides descriptive terminology to be used for adverse event reporting in clinical trials. A brief definition is provided to clarify the meaning of each adverse event (AE) term. To increase the accuracy of AE reporting, all adverse event terms in CTCAE, Version 4.03 have been correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA) terms.

CTCAE, Version 4.03 grading refers to the severity of the AE. CTCAE Grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Grade	CTCAE Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.[b]
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to adverse event.

ADL = activities of daily living, CTCAE = Common Terminology Criteria for Adverse Events, NCI = National Cancer Institute.
a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Adapted from the Cancer Therapy Evaluation Program, NCI. CTCAE v4.03. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (Accessed 25 Jun 2015).

For further details regarding MedDRA, refer to the MedDRA website at: http://www.meddra.org/. CTCAE, Version 4.03 is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html (Accessed 25 Jun 2015).

Appendix 3 Eastern Cooperative Oncology Group Performance Status and Karnofsky Performance Status Scale

ECOG[a]		Karnofsky[b]	
Score	**Criterion**	**%**	**Criterion**
0	Normal activity	100	Normal; no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Symptoms but ambulatory	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self; unable to carry on normal activity or do active work
2	In bed <50% of time	60	Requires occasional assistance but is able to care for most of his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed >50% of time	40	Disabled, requires special care and assistance
		30	Severely disabled; hospitalization is indicated though death is not imminent
4	100% bedridden	20	Very sick; hospitalization is necessary
		10	Moribund; fatal processes progressing rapidly
5	Dead	0	Dead

ECOG = Eastern Cooperative Oncology Group.

a: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

b: Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. Cancer. 1984;53:2002-2007.

Appendix 4 Pharmacokinetic Sample Collection, Handling, and Shipping

Blood Samples

Samples will be processed following the procedures below. Each plasma sample will be identified by protocol number, subject number, nominal day and time of sampling, and specimen matrix.

1. Draw blood samples from the median antebrachial vein and transferred into tubes containing sodium heparin.
2. Mix the blood and anticoagulant by gently inverting the tube 8 to 10 times and then place on water ice (crushed ice).
3. Within approximately 30 minutes of collection, centrifuge samples for 15 minutes at 2500 rpm at 4 °C.
4. Pipette the separated plasma equally, at least 1.5 mL each, into two 5 mL polypropylene tubes (Tubes marked as A and B). If the required volume of blood cannot be collected, a minimum of 1.5 mL of plasma must be transferred into Tube A and the remaining volume transferred to Tube B.
5. Store samples in an upright position at approximately –20 °C until samples are transferred for analysis to the designated bioanalytical laboratory.
6. After plasma separation, the remaining buffy coat and red blood cell layers should be discarded by the study institution in a proper manner.

Urine Samples (for Metabolite Profiling)

1. Subjects must void their urine just prior to the administration of study drug.
2. Urine will be collected in containers. During each collection period, the urine samples will be stored in a refrigerator at approximately 4 °C.
3. At the end of each collection interval, weight the collected urine and measure total volume of urine. Record the total volume in the case report form.
4. Mix the contents of each urine container gently to obtain a homogeneous solution.
5. Transfer approximately an aliquot of 8 mL each into the 13-mL polypropylene tubes (Tubes marked as A and B).
6. Store urine samples in an upright position at approximately -20 °C until samples are transferred for analysis to the designated bioanalytical laboratory.
7. The remaining urine will be appropriately discarded by the study institution in a proper manner.

Appendix 5 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamics, pharmacogenomics (PG) (separate consent required), and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or noncoding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the pharmacodynamic, PG, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for pharmacodynamic, PG, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic deoxyribonucleic acid (DNA) blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or ribonucleic acid extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the Sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the Sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The Sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the International Council for Harmonisation E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, H3 Biomedicine will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All pharmacodynamics and other biomarker samples will be single-coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identification [ID]) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical study will be cleaned of subject identifying information and linked by use of the sample ID "key."

The Sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The Sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the Sponsor
- Independent ethics committees or institutional review boards that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which may include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include

summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the pharmacodynamics, PG, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians.

If at any time, pharmacodynamics, PG, and/or other biomarker results are obtained that may have clinical relevance, Institutional Review Board/Independent Ethics Committee review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments (CLIA)-certified setting will be required. Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

Appendix 6 Child Pugh Classification Scoring

1.*	Child Pugh Classification Assessment [Child Pugh classification Assessment]	Not Done Done, Enter Date of Assessment Req / Req / Req (2016-2020)
2.	Total Serum Bilirubin [Total Serum Bilirubin]	Bilirubin <2 mg/dL (1 point) Bilirubin 2 to 3 mg/dL (2 points) Bilirubin >3 mg/dL (3 points)
3.	Serum Albumin [Serum Albumin]	Albumin >3.5 g/dL (1 point) Albumin 2.8 to 3.5 g/dL (2 points) Albumin <2.8 g/dL (3 points)
4.	INR [INR]	INR <1.70 (1 point) INR 1.7 to 2.30 (2 points) INR >2.30 (3 points
5.	Ascites [Ascites]	Absent (1 point) Mild (2 points) Moderate (3 points)
6.	Encephalopathy [Encephalopathy]	Grade 0: Normal consciousness, personality, neurological examination, electroencephalogram (1 point) Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps (cycles per second) waves (2 points) Grade 2: Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves (2 points) Grade 3: Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves (3 points) Grade 4: Unrousable, coma, no personality/behaviour, decerebrate, slow 2 to 3 cps deactivity (3 points)
7.	Child Pugh Score [read-only] [Child Pugh Score]	
8.	Child-Pugh classification [read-only] [Child-Pugh classification]	Child Pugh Class A : 5 to 6 points Child Pugh Class B : 7 to 9 points Child Pugh Class C : 10 to 15 points

CPS = cycles per second, INR = International Normalized Ratio.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: H3B-6527-G000-101

Study Protocol Title: An Open-Label Multicenter Phase 1 Study to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of H3B-6527 in Subjects With Advanced Hepatocellular Carcinoma

Investigational Product Name: H3B-6527

IND Number: 128686

EudraCT Number: 2016-001915-19

SIGNATURES

PPD

H3 Biomedicine, Inc.

10·5·20

Date

PPD

Oncology Business Group
Eisai, Inc.

06 OCT 2020

Date

INVESTIGATOR SIGNATURE PAGE

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

<Name of institution>

Medical Institution

<Name, degree(s)>

Investigator	Signature	Date